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Research article

The effect of intermittent hypoxia-normoxia training on exercise metabolism during a multi-component high-intensity interval training

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Abstract

Over the last few decades, there has been a significant increase in the scientific community's interest in IHNT, fueled by accumulating evidence of its therapeutic potential for enhancing athletic performance, cardiovascular disease, neurodegenerative conditions, and metabolic disorders. The aim of the study was to examine the acute metabolic and physiological impacts of intermittent hypoxia–normoxia training (IHNT), multicomponent high-intensity interval training (m-HIIT), and their combination in healthy people. Twelve physically active males participated in three randomized crossover trials: IHNT, m-HIIT, and a combination of IHNT and m-HIIT. Blood samples were taken before, immediately after, 1 hour after, and 3 hours after the intervention to assess the metabolic markers. Cardiorespiratory responses were monitored over time. IHNT produced a distinct hypoxic stimulus, as seen by decreased arterial oxygen saturation (SpO_2), an elevated heart rate (HR) during hypoxic cycles, and increased levels of Hypoxia-Inducible Factor-1α (HIF-1α). IHNT caused small, short-lived rises in glucose and albumin levels, but it didn't affect insulin sensitivity or lipid indicators. Conversely, m-HIIT and the combined trial resulted in significant acute elevations in glucose, insulin, Homeostasis model assessment index of insulin resistance (HOMA-IR), glycerol, and lactate, indicating considerable metabolic and glycolytic stress. During recuperation, triglyceride levels decreased, although vitamin D and urea demonstrated trial-specific temporal variations. These results indicate that a single trial of IHNT activates metabolic and physiological responses by increasing HIF-1a. levels, HR, glucose, and reducing SpO_2. Additionally, m-HIIT enhances glycolysis, and a trial of exercise following IHNT modifies carbohydrate and lipid levels, stimulated by glycogenolysis and gluconeogenesis.

Keywords: IHNT, m-HIIT, Glycolysis, Glucose homeostasis, Vitamin D

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Introduction

Intermittent hypoxia training (IHNT) provides a controlled, therapeutic approach that simulates the physiological stress experienced at high altitude by alternating between periods of normoxic recovery and repetitive exposure to reduce oxygen availability (Serebrovskaya and Xi, 2016). IHNT, in contrast to chronic continuous hypoxia, which may cause pathological alterations, uses brief hypoxic stimuli to initiate beneficial metabolic remodeling without the negative impacts associated with prolonged oxygen deprivation (Wang et al., 2024). Over the last decades, there has been a significant increase in the scientific community's interest in IHNT, which has been fueled by the accumulation of evidence regarding its therapeutic potential for athletic performance enhancement, cardiovascular disease, neurodegenerative conditions, and metabolic disorders (Astorino et al., 2015; Serebrovska et al., 2017). Cellular oxygen-sensing mechanisms are triggered by hypoxic stress, and these mechanisms then trigger transcriptional and post-transcriptional programs that control metabolism, angiogenesis, erythropoiesis, and cell survival (Damiani et al., 2018; Haase, 2013; Semenza, 2000) These adaptive responses are influenced by the extensive alteration in metabolism that affects glucose utilization, lipid oxidation, mitochondrial function, and energy substrate preference, and are controlled by major genetic factors, particularly Hypoxia-Inducible Factor-1α (HIF-1α) (Afina et al., 2021; Maxwell, 2001). Specifically, in patients with prediabetes, a 3-week IHNT program improved glucose homeostasis, reducing fasting blood glucose levels, with the most pronounced effects observed 1 month after the intervention (Serebrovska et al., 2019, 2017). Furthermore, changes in glucose and insulin levels were significantly reduced following a 60-minute bout of hypoxic exercise in individuals with type 2 diabetes compared with normoxic exercise (Mackenzie et al., 2012, 2011). However, these effects were not observed after only 20 minutes of hypoxic exercise (Van Hulten et al., 2021). Ultimately, De Groote et al. (2018) demonstrated that, in obese adolescents, plasma insulin levels were substantially reduced during an oral glucose tolerance test, and glucose tolerance improved after six weeks of hypoxic training but not normoxic training (De Groote et al., 2018). Glazachev et al. (2017) and Afina et al. (2021) found that IHNT improves lipid profile by reducing triglycerides and total cholesterol after a 3-5-week program. Furthermore, hypoxic exposure can be combined with exercise to enhance metabolic activity, including lactate, cortisol, lipids, and lipoproteins (Czuba et al., 2011; Kon et al., 2012).

In response to the elevated energy demands of working muscles, exercise induces rapid and coordinated metabolic adaptations to maintain homeostasis (Henke et al., 2018). Numerous researchers studying team sports have reported significant increases in free fatty acids, glucose, and glycerol following matches, thereby stimulating a high rate of lipolysis (Ben Abdelkrim et al., 2009; Chatzinikolaou et al., 2008; Petridou et al., 2017). Insulin resistance in skeletal muscle leads to the transfer of glucose to the liver for de novo lipogenesis (fatty acid production) (Van Der Windt et al., 2018). In addition to being stored as triglycerides, free fatty acids (FFAs) are considered the metabolically and immunologically active form of fat, contributing to cellular damage and inflammation (Alkhouri et al., 2009; Nikolaidis and Mougios, 2004). According to Mougios et al. (1995), the lowest lactic acid concentration was observed after 60 minutes of a handball game, compared with the mid-game point, indicating reduced carbohydrate utilization in the second half. On the other hand, plasma glycerol and all non-esterified fatty acids showed a different pattern, successive increases in both halves of the game, indicating continuous stimulation of lipolysis throughout the match. In the study by Chatzinikolaou et al. (2008), increases in non-esterified free fatty acids, insulin, and glycerol were observed in obese individuals following 30 minutes of circuit training. In addition, high-intensity interval training (HIIT) has become increasingly popular as an effective exercise method for improving cardiorespiratory fitness, metabolic regulation, and a variety of other health indices (Bogdanis et al., 2013; Protopapa et al., 2025). Bogdanis et al. (2022a, 2022b) showed that glucose, insulin, and blood lactate levels increased following acute HIIT, particularly in the intensive exercise group.

The roll-out of an extensive variety of hypoxia protocols in both healthy individuals and diseased patients has garnered significant interest in recent years, as a result of the documented benefits associated with intermittent hypoxia (Burtscher et al., 2004). Metabolic evaluations in long-term hypoxia programs are the main focus of most studies. However, there is a lack of research on the effects of metabolic markers during acute interventions and in the post-intervention period. The metabolic responses to IHNT can be leveraged to improve health and performance, similar to those induced by exercise (Katayama et al., 2003). Nevertheless, the data on the effects and potential variation in exercise on metabolic markers following hypoxia have not been sufficiently investigated, so additional research is necessary to characterize the adaptations and responses to IHNT combined with exercise. Consequently, the objective of this study was to examine the separate and combined effects of intermittent hypoxia-normoxia and multi-component high-intensity interval training on metabolism markers of glycerol (Gly), albumin (Al), glucose (G), lactic acid (La), insulin (In), Homeostasis model assessment Index of insulin resistance (Homa-IR), urea (U), and vitamin D 25(OH-VD), in healthy adults. During a single fitness session, multi-component high-intensity interval training (m-HIIT) alternates between resistance exercises and cardiovascular exercises, thereby fostering both cardiorespiratory and neuromuscular adaptations (Jung et al., 2020).

Materials and methods

Subjects

An a priori power analysis (F tests, repeated-measures ANOVA, within–between interaction) was conducted using G*Power software (version 3.1.9.4). Assuming an effect size of f = 0.30, an alpha level of 0.05, and 95% power, the required sample size was determined to be 12 participants to detect statistically significant treatment effects across repeated measurements. Accordingly, 12 healthy male participants (age: 25.6 ± 5.8 years; height: 179.6 ± 10.5 cm; body mass: 82.6 ± 10.6 kg; body mass index: 25.6 ± 2.6 kg·m^{-2}) were recruited for the study. All participants were free from chronic diseases, had no current musculoskeletal injuries, and were not using any medications known to affect physical performance or cardiovascular function.

Exclusion criteria included the presence of acute physical or viral illness, intolerance to hypoxia, or medical conditions such as decompression sickness, epilepsy, cardiac arrhythmias, or the use of a pacemaker. Female participants were excluded to eliminate potential confounding effects of menstrual-cycle-related fluctuations in estrogen on physiological responses to intermittent hypoxia. Participants were instructed to maintain their usual dietary habits throughout the study. However, the use of vitamin C injections, high-dose vitamin C supplementation (>1000 mg·day^{-1}), or beta-blocker medications was not permitted.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Democritus University of Thrace (approval code: DUTH/EHDE/38819/323). All participants were fully informed about the purpose, procedures, and potential risks of the study prior to participation. Written informed consent was obtained from all participants before enrollment.

Experimental design

All participants completed three experimental protocols in a randomized crossover design at the Physical Performance Laboratory of the Department of Physical Education and Sport Science at Democritus University of Thrace between May and September 2024. All measurements were performed within the same time window, between 8:30 a.m. and 12:30 p.m. Each participant completed a detailed interview regarding wellness status, habitual physical activity, and any current medical conditions. Before enrollment, participants were fully informed about the benefits, risks, and potential discomforts associated with the study, and all provided written informed consent. Prior to the intervention, participants underwent baseline assessments, including resting blood sampling following an overnight fast, anthropometric measurements, and body composition analysis. In addition, participants were familiarized with the training protocols and experimental procedures. Subsequently, participants completed three experimental trials in a randomized crossover repeated-measures design: i) intermittent hypoxia–normoxia training (IHNT), ii) multicomponent high-intensity interval training (m-HIIT) (E.T.), and iii) a combined IHNT and m-HIIT trial (C.T.).

Venous blood samples were collected at four time points during each trial: before the intervention (pre), immediately after the intervention (post), and at 1 h and 3 h post-intervention (Figure 1). A 10-day washout period was implemented between trials to minimize potential carryover effects. All experimental trials were performed following an overnight fast. Participants were instructed to refrain from strenuous physical activity or exercise for at least 48 h prior to each trial and to consume only water until completion of the protocol.

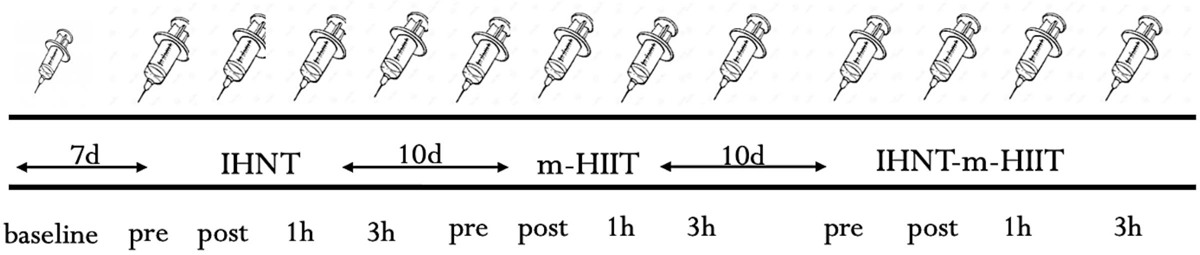

Figure 1: Schematic representation of the research trials; IHNT: Intermittent Hypoxia-Normoxia Training; m-HIIT: multicomponent High-Intensity Interval Training.

Experimental Protocols

Intermittent Hypoxia–Normoxia Training (IHNT)

The IHNT protocol consisted of three cycles of hypoxia and normoxia, each comprising 8 min of hypoxia (O_2: 10–12%) followed by 2 min of normoxia (O_2: 20%). The total session duration was 30 min. The IHNT protocol was designed to be comparable to the exercise protocol, involving 8 min of work followed by 2 min of rest. An altitude-simulation device (Celloxy-Tur, Rostock Germany) was used to deliver normobaric hypoxic air via a facemask. Participants were seated in recliners in a temperature-controlled, quiet environment. Throughout the session, peripheral oxygen saturation (SpO_2) and heart rate (HR) were continuously monitored using a finger pulse oximeter and a heart rate monitoring system (Polar Team Pro, Polar Electro, Kempele, Finland).

Multicomponent high-Intensity interval training (m-HIIT) (E.T.)

The m-HIIT protocol was a hybrid exercise intervention combining resistance and cardiovascular components, as previously described (Protopapa et al., 2025). The training session included an initial 6-min warm-up, followed by the main session and a 5-min cool-down. During the main session, participants completed three circuits of eight exercises using a 30 s:30 s work-to-rest ratio, with a 3-min rest period between circuits. The eight exercises were as follows: battle ropes, modified Olympic weightlifting, jumping jacks, planks, sit-ups combined with rowing, agility ladder drills, hip thrusts, and lateral steps. The m-HIIT session lasted 30 min, and participants were verbally encouraged to maintain the prescribed level of exertion throughout. Internal load was monitored using complementary physiological and perceptual measures, including heart-rate-derived indices and ratings of perceived exertion (RPE). Heart rate was continuously monitored throughout the session using a heart rate monitoring system (Polar Team Pro, Polar Electro, Kempele, Finland). Minimum, mean, and maximum heart rate values were extracted for each session. Cardiovascular internal load was quantified using two heart-rate-based approaches. Overall internal training load was assessed using the Training Impulse (TRIMP) model, calculated according to Banister's exponential formulation (Calvert et al., 1976). TRIMP was computed by integrating exercise duration and relative heart rate intensity using the following equation (1):

$$\text{"TRIMP"}=\sum (t_i \times HR_{rel,i} \times e^{k \times HR_{rel,i}}) \quad (1)$$

where t_i represents the time (in minutes) accumulated at a given heart rate intensity, HR_{rel} is the relative heart rate calculated as $(HR-HR_{rest})/(HR_{max}-HR_{rest})$, and k is a sex-specific weighting constant (1.92 for males and 1.67 for females). Perceived exertion was assessed 30 min following the completion of the training session using the Borg CR-10 scale (Borg, 1998). Training volume was quantified as total repetitions, defined as the sum of all repetitions completed across exercises within the circuit.

Lactate is determined by obtaining a small blood sample via finger prick and analyzing it with a handheld analyzer (Mohr et al., 2016).

Combination trial (C.T.)

During C.T., participants completed the IHNT trial both initially and immediately after participating in the m-HIIT trial, as described above.

Blood sampling and biochemical analysis

Blood samples were collected from an antecubital vein by a qualified nurse at four time points during each trial: at rest (Pre), immediately after the intervention (Post), and 1 h and 3 h post-intervention. A 12 mL blood sample was allowed to coagulate at ambient temperature, then centrifuged at 1500 g for 15 min at 4 °C to obtain serum. Serum samples were analyzed for glycerol (Gly), albumin (Alb), 25-hydroxyvitamin D [25(OH)D], glucose (Glu), insulin (Ins), urea (U), and hypoxia-inducible factor-1α (HIF-1α).

A portion of the serum was used immediately to measure glucose, urea, triglycerides, and albumin using a clinical chemistry analyzer (HumanStar 2000), while the remaining sample was divided into aliquots and stored at −80 °C for subsequent analyses.

Serum insulin and cortisol were measured according to the manufacturer's instructions, and 25(OH)D was determined using an MPQuanti® immunofluorescence analyzer. HIF-1α and glycerol concentrations were measured using commercially available solid-phase enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions (Elabscience, Houston, Texas, USA). HOMA-IR was calculated from fasting glucose and fasting insulin concentrations using the following formula: [glucose (mg/dL) × insulin (μIU/mL)] / 405, as originally described by Mathews et al. (1985).

An additional 2.5 mL blood sample was collected into EDTA-containing tubes for complete blood count analysis and determination of hemoglobin concentration, which was measured immediately using an automated hematology analyzer (Sysmex KX-21, Kobe, Japan).

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics (version 30.0; IBM Corp., Armonk, NY, USA). Data are presented as mean ± standard deviation (SD). Normality was assessed for each outcome using the Shapiro–Wilk test and visual inspection of Q–Q plots and histograms. As no substantial deviations from normality were identified, parametric procedures were applied.

Differences between E.T. and C.T. were analyzed using paired samples t-tests. Effect sizes for paired comparisons were calculated as Cohen's d based on the standard deviation of the paired differences, with values of 0.20, 0.50, and 0.80 indicating small, medium, and large effects, respectively.

Changes over time during the IHNT trial (baseline, pre, post, 1 h post, and 3 h post) were analyzed using one-way repeated-measures ANOVAs. To evaluate the combined effects of time and trial (IHNT vs C.T. and E.T. vs C.T.), two-way repeated-measures ANOVAs (time × trial) were conducted. For repeated-measures models, the assumption of sphericity was evaluated using Mauchly's test for within-subject effects involving more than two levels (i.e., time and time × trial). When sphericity was violated, Greenhouse–Geisser corrections were applied to the degrees of freedom, and the corrected statistics were reported. Significant effects were followed by Bonferroni-adjusted pairwise comparisons. When a significant time × trial interaction was detected, post hoc testing focused on simple effects, including comparisons across time within each trial and/or comparisons between trials at each time point, with Bonferroni adjustment.

Effect sizes for ANOVA models are reported as partial eta squared (ηp^2) and were interpreted as small (0.01), medium (0.06), and large (0.14). Statistical significance was set at $p < 0.05$ (two-tailed) for all analyses.

Results

Responses to the IHNT trial

Time-dependent changes in SpO2, HR and HIF-1α

Two-way repeated-measures ANOVAs were conducted to examine the effects of time, trial (IHNT vs. C.T.), and their interaction on SpO_2, average heart rate, and HIF-1α. The assumption of sphericity was violated for the time factor in all variables; therefore, Greenhouse–Geisser-corrected values are reported. No significant time × trial interactions were observed for SpO_2, average heart rate, or HIF-1α (all p-values$\geq$ 0.273), indicating similar temporal responses across the two trials. Likewise, no significant main effects of trial were detected for any variable (all $p \geq 0.218$).

However, significant main effects of time were found for all three variables. SpO_2 changed significantly over time, $F(1.79, 19.72) = 29.58$, $p < 0.001$, $\eta p^2 = 0.73$, with Bonferroni-adjusted comparisons showing lower values during hypoxic phases than during rest and the corresponding normoxic phases. Average heart rate also varied across time, $F(2.95, 32.48) = 12.13$, $p < 0.001$, $\eta p^2 = 0.52$, with higher values observed during hypoxic phases than at rest and during selected normoxic periods. Similarly, HIF-1α exhibited a significant main effect of time, $F(1.00, 11.01) = 8.56$, $p = 0.014$, $\eta p^2 = 0.44$, with higher post-intervention values (IHNT: 17.8 ± 18.8; C.T.: 14.1 ± 11.5 pg/mL) than at baseline (IHNT: 7.4 ± 5.1; C.T.: 7.3 ± 7.8 pg/mL) and pre-intervention (IHNT: 7.4 ± 5.0; C.T.: 7.4 ± 7.0 pg/mL). Results are presented in Tables 1 and 2.

Time-dependent changes in Hgb

A one-way repeated-measures ANOVA was conducted to examine changes over time (baseline, pre, post, 1 h, and 3 h) during the IHNT trial. Mauchly's test indicated that the assumption of sphericity was violated; therefore, Greenhouse–Geisser corrections were applied. Hemoglobin (HGB) showed a significant main effect of time, $F(1.55, 17.06) = 6.66$, $p = .011$, $\eta p^2 = 0.38$. Follow-up pairwise comparisons indicated a significant reduction in HGB from baseline (15.7 ± 1.0 g/dL) to post-trial (15.12 ± 0.8 g/dL) ($p = 0.019$), as well as from pre-trial (15.7 ± 1.0 g/dL) to post-trial (15.12 ± 0.8 g/dL) ($p = .013$). Results are presented in Table 3

Time-dependent changes in metabolites

A series of one-way repeated-measures ANOVAs was conducted to examine changes across time (baseline, pre, post, 1 h, and 3 h) in metabolic variables during the IHNT trial. The assumption of sphericity was violated for all variables; therefore, Greenhouse–Geisser–corrected values are reported.

Glucose and albumin showed a significant main effect of time ($p< 0.001$). Follow-up contrasts showed a rise in glucose levels to post (81.57±6.5 mg/dL) and post-1h (83±6.63 mg/dL) compared to baseline (75.33±4.94 mg/dL) and pre (75.77±4.97 mg/dL). Albumin indicated significant increases from post (4.7±0.2 g/dL) to post-1h (4.9±0.2 g/dL) and decreases from baseline (5±0.2 g/dL) and pre (4.9±0.2 g/dL) to post (4.7±0.2 g/dL).

In contrast, no significant main effects of time were found for insulin, glucose, HOMA-IR, triglycerides, vitamin D, or urea (all $p> .05$). Results are presented in Table 4.

Table 1: Two-way repeated-measures ANOVA for SpO_2 & HR at IHNT trial and C.T.

Variable	Rest	Hypoxia 1	Normoxia 1	Hypoxia 2	Normoxia 2	Hypoxia 3	Normoxia 3	ηp²
SpO_2 (%)	96.8±1.6	86.4±2.8*,#	90.1±4.0*	85.7±2.7*,#	90.3±3.5	88±3.3*,#	92.8±4.6	0.73
	97±1.4	86±1.4*,#	90.8±2.2	85.7±2.9*,#	90.4±3.1	86.9±2.9	92.7±3.1	
Average HR (bpm)	66±8	70.7±9.4*,#	62.8±7.1	67.5±9*	62.9±8	69±10.2*	64.7±10.3	0.52
	60.8±8.8	69.8±9.2*,#	63.1±7.3	67±8.3*	61.6±7.5	68±9.3*	64±7.4	

*Significant difference with baseline ($p<0.001$); #indicates significant difference between Hypoxia-Normoxia during cycle ($p<0.001$); SpO_2: peripheral oxygen saturation; IHNT: Intermittent Hypoxia Normoxia Training; C.T.: combined trial; values are presented as Mean±SD.

Table 2: Two-way repeated measures ANOVA for HIF-1a at IHNT and C.T.

Variable	Baseline	pre	post	ηp²
HIF-1a (pg/mL)	7.4±5.1*	7.4±5*	17.6±18.8	0.44
	7.3±7.8*	7.4±7.8*	14.1±11.5	

*Significant difference with post ($p<.001$); HIF-1a: hypoxia-inducible factor-1a; IHNT: Intermittent Hypoxia Normoxia Training; C.T.: combined trial; values are presented as Mean±SD.

Table 3: One-way repeated-measures ANOVA (IHNT trial) across time.

Variable	Baseline	pre	post	1h	3h	ηp²
HGB (g/dL)	15.7±1*	15.7±1*	15.12±0.8	15.25±0.7	15.3±0.8	0.38

*Significant difference with post (p<.05); IHNT: Intermittent Hypoxia Normoxia Training; HGB: hemoglobin; pre: before trial; post: immediately after trial; 1h: 1h after trial; 3h: 3h after trial; p-value: probability value; ηp^2: partial eta squared; values are presented as Mean±SD.

Table 4: One-way repeated-measures ANOVA across time in IHNT trial.

Variable	Baseline	Pre	Post	1h	3h	p-value	ηp²
Glucose (mg/dL)	75.33 ± 4.94	75.77 ± 4.97	81.57± 6.58[a,b]	83.00 ± 8.75a,[b]	80.20 ± 6.63	0.001	0.048
Insulin (µIU/mL)	6.71 ± 2.51	6.61 ± 2.47	7.43 ± 3.11	6.45 ± 2.25	5.92 ± 2.14	0.128	0.147
HOMA-IR	1.25 ± 0.45	1.24 ± 0.45	1.48 ± 0.56	1.31 ± 0.42	1.18 ± 0.43	0.226	0.471
Triglycerides (mg/dL)	81.13 ± 28.79	81.13 ± 28.79	67.54 ± 18.24	71.50 ± 19.99	66.58 ± 20.71	0.077	0.24
Albumin (g/dL)	5±0.2[c]	4.9±0.2[c]	4.7±0.2	4.9±0.2[c]	5±0.2	< 0.001	0.46
Vitamin D (ng/mL)	37.42 ± 16.99	37.85 ± 17.08	37.81 ± 17.05	38.42 ± 17.07	38.41 ± 16.26	0.852	0.03
Urea (mg/dL)	39.08 ± 7.02	38.82 ± 7.19	37.63 ± 7.10	36.44 ± 6.86	35.29 ± 6.49	0.460	0.07

[a]significant difference with baseline; [b]signicicant difference; [c]significant difference with post; IHNT: Intermittent Hypoxia Normoxia Training; HOMA-IR: Homeostasis model assessment index of insulin resistance; pre: before trial; post: immediately after trial; 1h: 1h after trial; 3h: 3h after trial; p-value: probability value; ηp^2: partial eta squared; values are presented as Mean±SD.

Responses to E.T. and C.T.

Differences between pre- and post in E.T. and C.T. variables

Paired-samples tests were conducted to compare performance and heart-rate variables between the exercise trial and combined trial (n = 12). No significant differences were observed between trials for average heart rate, $t(11) = -0.40$, $p = 0.700$, minimum heart rate, $t(11) = 0.08$, $p = 0.942$, maximum heart rate, $t(11) = -1.20$, $p = 0.256$, training load, $t(11) = 0.30$, $p = .771$, or rating of perceived exertion, $t(11) = 0.83$, $p = 0.422$. Results are presented in Table 5.

Lactate changes during cycles in E.T. and C.T.

A two-way repeated-measures ANOVA was conducted to examine the effects of time (pre, 1st cycle, 2nd cycle, and 3rd cycle) and trial (exercise trial vs. combined trial) on blood lactate concentrations. Mauchly's test indicated that the assumption of sphericity was not violated for time, $W = 0.747$, $p = 0.771$; sphericity-assumed results are reported.

The time × trial interaction was not significant, $F(3, 30) = 0.46$, $p = .712$, $\eta p^2 = .04$, indicating similar temporal responses across the two trials. No significant main effect of trial was found, $F(1, 10) = 0.12$, $p = .737$, $\eta p^2 = .01$. There was a significant main effect of time, $F(3, 30) = 71.26$, $p < .001$, $\eta p^2 = .88$, demonstrating substantial increases in lactate across the exercise cycles. Bonferroni-adjusted post hoc comparisons showed that lactate concentrations at the 1st, 2nd, and 3rd cycles were significantly higher than pre-exercise values (all $p < 0.001$), whereas no significant differences were observed among the three exercise cycles. Results are presented in Table 6.

Table 5: Paired-samples t tests comparing exercise trial- and combined trial values.

Variable	Exercise (M ± SD)	Combined (M ± SD)	t(df)	p-value	Cohen's d
Average HR (bpm)	132.7 ± 9.7	133.7 ± 8.5	−0.40 (11)	0.7	−0.12
Minimum HR(bpm)	71.8 ± 9.7	71.6 ± 9.7	0.08 (11)	0.942	0.02
Maximum HR(bpm)	170.7 ± 11.3	173.6 ± 7.7	−1.20 (11)	0.256	−0.35
Training load	48.7 ± 17.7	47.6 ± 9.9	0.30 (11)	0.771	0.09
RPE	5.3 ± 2.1	4.8 ± 2.3	0.83 (11)	0.422	0.24

Values are presented as mean±SD. Cohen's d is based on the standard deviation of the paired differences; RPE: Rate of Perceived Exertion; HR: heart rate.

Table 6: Two-way repeated-measures ANOVA for lactate (time × trial).

Variable	pre	1st cycle	2nd cycle	3rd cycle	ηp²
Lactate (mmol/L)	1±0	12.8±4.4*	13.8±4.4*	12.8±4.9*	0.88
	1±0	12.7±5*	13.7±3.7*	14.3±4.5*	

*Significant difference with pre (p<0.001); pre: before trail; 1st cycle: 1st cycle of exercise trial; 2nd cycle of exercise trial; 3rd cycle of exercise trial; ηp²: eta squared; values are presented as Mean±SD.

Metabolites in E.T. and C.T.

Two-way repeated measures ANOVAs were conducted to examine the effects of time (baseline, pre, post, 1 h, and 3 h), trial (E.T. vs. C.T.), and the time × trial interaction on metabolic variables.

Significant time × trial interactions were observed for vitamin D, $F(2.43, 26.71) = 4.35$, $p = 0.005$, $\eta p^2 = 0.284$, and urea, $F(4, 44) = 2.95$, $p = .030$, $\eta p^2 = 0.21$, indicating trial-specific temporal responses. For vitamin D, values increased in both trials from baseline (E.T.: 38.9 ± 16.7; C.T.: 38.0 ± 16.4 ng/mL) and pre (E.T.: 39.3 ± 16.8; C.T.: 38.7 ± 18.8 ng/mL) to post (E.T.: 45.6 ± 16.7; C.T.: 43.1 ± 19.2 ng/mL), 1 h (E.T.: 48.4 ± 17.5; C.T.: 40.3 ± 15.2 ng/mL), and 3 h (E.T.: 48.1 ± 16.4; C.T.: 40.2 ± 18.1 ng/mL), with a greater and more sustained increase in E.T. than in C.T. For urea, trial-specific changes were also observed, although these responses differed in magnitude and direction across time points between E.T. and C.T.

For the remaining variables, no significant time × trial interactions were detected (all $p > .05$). Significant main effects of time were observed for HOMA-IR, glucose, insulin, triglycerides, albumin, and glycerol (all $p < 0.05$), indicating temporal changes irrespective of trial. Bonferroni-adjusted comparisons showed that glucose increased from baseline (E.T.: 72.0 ± 7.6; C.T.: 73.0 ± 7.7 mg/dL) and pre (E.T.: 73.5 ± 7.8; C.T.: 77.0 ± 8.6 mg/dL) to post (E.T.: 92.15 ± 12.7; C.T.: 92.4 ± 14.8 mg/dL), and then declined at 1 h (E.T.: 79.7 ± 7.0; C.T.: 77.8 ± 6.0 mg/dL) and 3 h (E.T.: 77.8 ± 6.6; C.T.: 80.0 ± 7.5 mg/dL). Insulin was higher post-intervention (E.T.: 9.75 ± 4.7; C.T.: 8.3 ± 3.2 μIU/mL) than at baseline (E.T.: 6.4 ± 3.6; C.T.: 5.6 ± 2.7 μIU/mL), and lower values were observed at 3 h post-intervention (E.T.: 4.8 ± 2.1; C.T.: 5.2 ± 2.3 μIU/mL) compared with both post-intervention and 1 h post-intervention (E.T.: 6.9 ± 2.7; C.T.: 6.9 ± 3.3 μIU/mL). Similarly, HOMA-IR increased from baseline (E.T.: 1.13 ± 0.6; C.T.: 0.9 ± 0.4) and pre (E.T.: 1.15 ± 0.6; C.T.: 1.6 ± 0.6) to post (E.T.: 2.3 ± 1.4; C.T.: 1.9 ± 0.7), and then decreased at 1 h (E.T.: 1.35 ± 0.6; C.T.: 1.3 ± 0.6) and 3 h (E.T.: 0.9 ± 0.4; C.T.: 1.0 ± 0.5).

In addition, triglyceride concentrations were significantly lower at 3 h post-intervention than immediately post-intervention in C.T. (66 ± 19.5 vs. 85 ± 22 mg/dL). Albumin increased from earlier to later time points, rising in E.T. from baseline (4.75 ± 0.34 g/dL) and pre (4.75 ± 0.2 g/dL) to 3 h (5.0 ± 0.2 g/dL), and in C.T. from baseline (4.75 ± 0.34 g/dL) and pre (4.76 ± 0.2 g/dL) to post (5.0 ± 0.2 g/dL). Glycerol also showed a significant main effect of time, $F(1, 11) = 10.62$, $p = .008$, $\eta p^2 = 0.49$.

Bonferroni-adjusted comparisons indicated that glycerol concentrations were significantly higher post-intervention (E.T.: 0.075 ± 0.04; C.T.: 0.10 ± 0.07 mmol/L) than at baseline (E.T.: 0.03 ± 0.02; C.T.: 0.03 ± 0.02 mmol/L) and pre (E.T.: 0.03 ± 0.03; C.T.: 0.05 ± 0.05 mmol/L). Results are presented in Figures 2, 3, 4, 5–6.

Discussion

This research examined the acute metabolic and physiological responses to intermittent hypoxia–normoxia training (IHNT), multicomponent high-intensity interval training (m-HIIT), and their combination in healthy people. The main findings indicate that the IHNT trial induced an independent hypoxic stimulus, as indicated by significant reductions in SpO_2, increases in heart rate during hypoxic cycles, and elevated plasma HIF-1α levels immediately after the IHNT trial.

Metabolically, IHNT contributed to short-term increases in blood glucose and albumin, but there were no major changes in insulin, HOMA-IR, TG, vitamin D, and urea. In addition, both E.T. and C.T. induced significant acute elevations in glucose, insulin, HOMA-IR, glycerol, and lactate, indicating notable metabolic and glycolytic stress; in contrast, a significant decrease in triglycerides was observed three hours after the trials. Vitamin D and urea showed time × trial interaction in temporal responses.

Vitamin D decreased following the C.T., while it showed an upward trend following the E.T. Urea's trend was downward; it appeared to decrease at 1 and 3 hours following the two trials, with a more pronounced reduction after E.T., suggesting specific metabolism pathways between acute exercise and combined IHNT and exercise exposure.

In the IHNT trial, an elevated plasma concentration of HIF-1α was observed following hypoxic exposure, according to previous studies, indicating that hypoxia-sensitive molecular pathways can be quickly activated even after short periods of low oxygen levels, and is the main transcription activator that senses oxygen and helps cells adjust to low oxygen levels (Millet et al., 2016; Muangritdech et al., 2020; Serebrovskaya and Xi, 2016). Semenza et al. (1999) have characterized HIF-1α as a pivotal regulator of metabolic remodeling in response to hypoxic stress, influencing glucose utilization and lipid metabolism (Semenza, 1999). From an operational perspective, this finding confirms that the IHNT trial used in the current investigation delivered an efficiently hypoxic dose without imposing excessive cardiovascular stress. The heart rate served as a compensatory mechanism for the shortage of oxygen, increasing in hypoxic phases, with higher values at 1rst cycle (70.7±9.4 bpm) and decreasing in normoxic (1rst cycle: 62.8±7.1 bpm), similar to Mahat et al. (2016) research, where HR ranged from 67.8±11.9 in normoxia to 71.7±11.6 in hypoxia phase (Mahat et al., 2016). In contrast, oxygen saturation decreased during hypoxic periods, with lower levels during the 1st cycle (86.4±2.8 %), followed by an increase during normoxic periods, with higher values during the last normoxic phase (92.8±4.6 %). These findings are also corroborated by Mahat et al. (2016) and prior research, which found that SpO_2 varied from 96.8±1.3% to 90.2±1.1% during a 6-hour hypoxic trial.

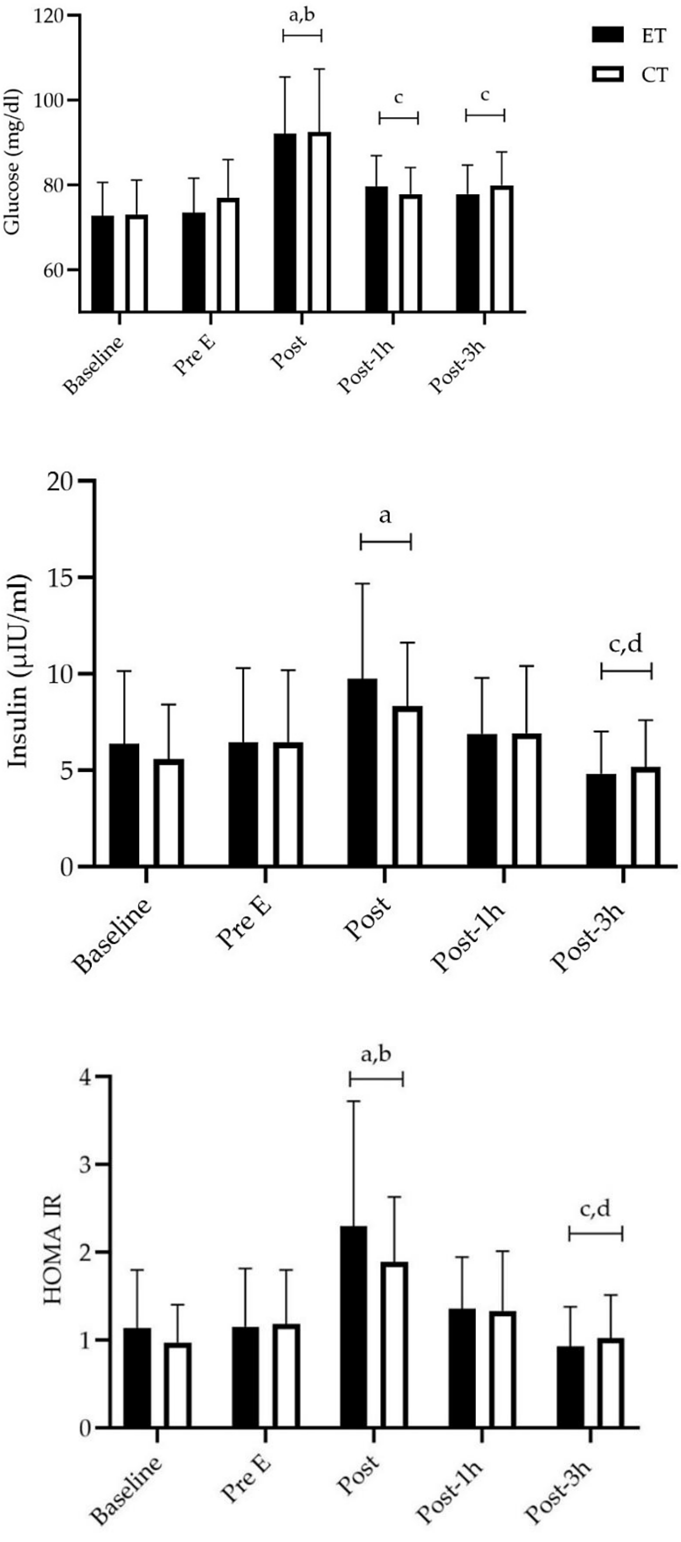

Figure 2: Glucose, insulin and HOMA-IR alterations across time at E.T. and C.T.; HOMA-IR: Homeostasis model assessment index of insulin resistance; pre E: before exercise trial; post: immediately after exercise trial; 1h: 1h after exercise trial; 3h: 3h after exercise trial; E.T.: exercise trial; C.T.: combined trial; a significant difference with baseline, [b]significant difference with pre E; [c]significant difference with post; [d]significant difference with post-1h; values are presented as Mean±SD.

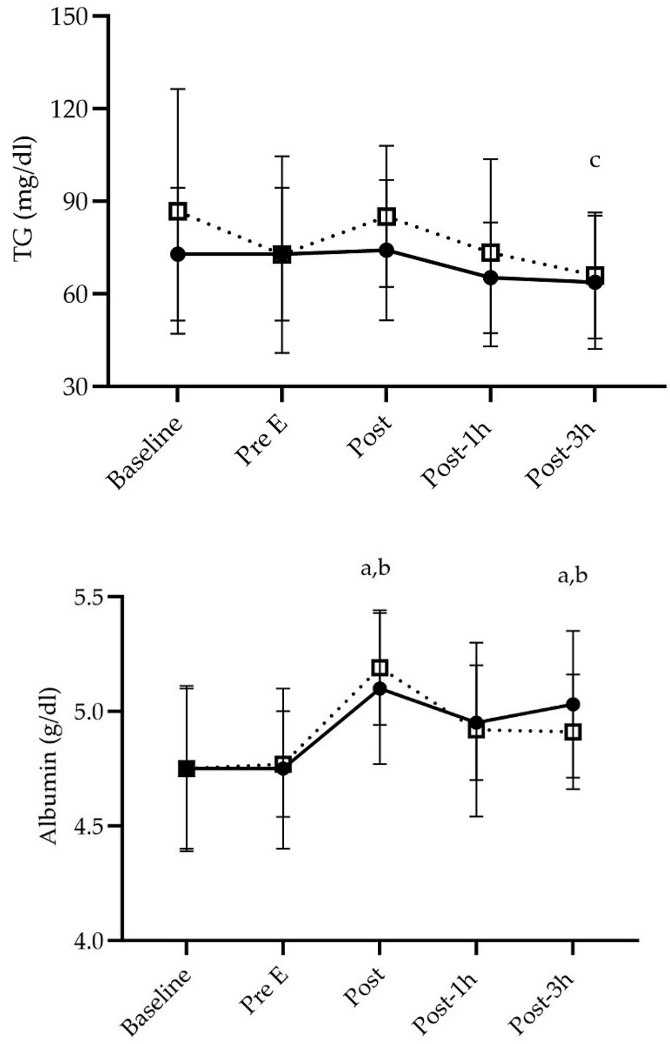

Figure 3: TG and albumin alterations across time at E.T. and C.T.; pre E: before exercise trial; post: immediately after exercise trial; 1h: 1h after exercise trial; 3h: 3h after exercise trial; E.T.: exercise trial; C.T.: combined trial; [b]significant difference with pre E; [c]significant difference with post; values are presented as Mean±SD.

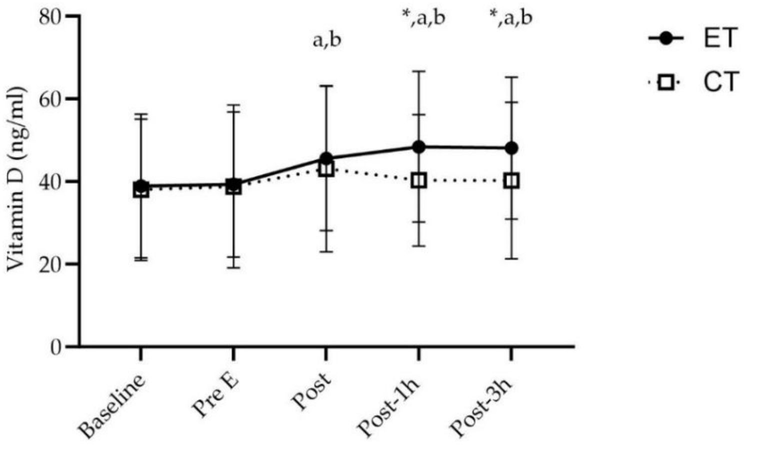

Figure 4: Vitamin-D alterations across time at E.T. and C.T.; pre E: before exercise trial; post: immediately after exercise trial; 1h: 1h after exercise trial; 3h: 3h after exercise trial; E.T.: exercise trial; C.T.: combined trial; *significant difference between trials; [a]significant difference with baseline; values are presented as Mean±SD.

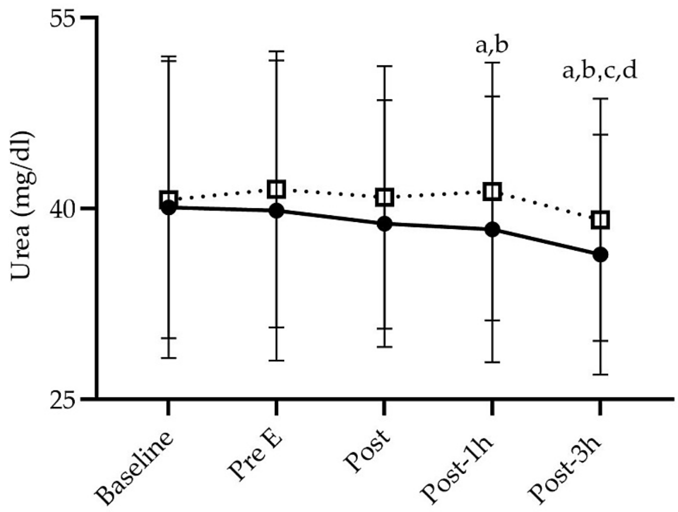

Figure 5: Urea alterations across time at E.T. and C.T.; pre E: before exercise trial; post: immediately after exercise trial; 1h: 1h after exercise trial; 3h: 3h after exercise trial; E.T.: exercise trial; C.T.: combined trial; [a]significant difference with baseline, [b]significant difference with pre E; [c]significant difference with post; [d]significant difference with post-1h; values are presented as Mean±SD.

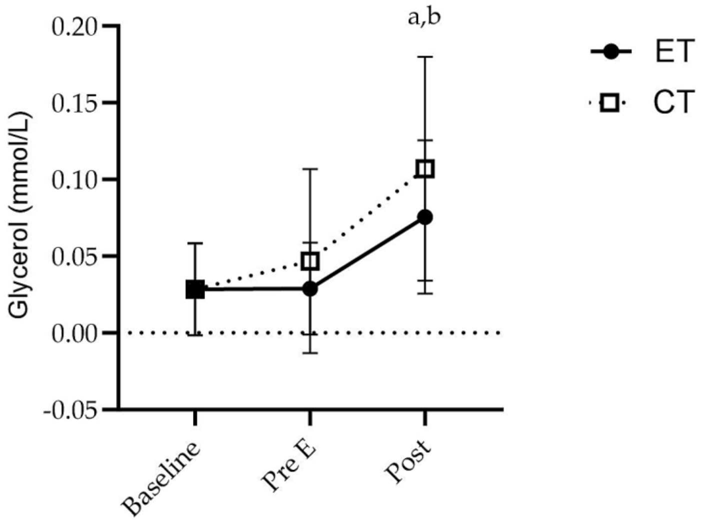

Figure 6: Glycerol alterations across time at E.T. and C.T.; pre E: before exercise trial; post: immediately after exercise trial; E.T.: exercise trial; C.T.: combined trial; [a]significant difference with baseline, [b]significant difference with pre E; values are presented as Mean±SD.

In contrast to metabolite alterations reported in other studies that demonstrated a decrease in glucose following 60 minutes of hypoxia, these results indicate an increase in glucose (Duennwald et al., 2013; Mackenzie et al., 2011; Van Der Windt et al., 2018). It is likely that the duration of hypoxic exposure is essential for glucose assimilation by muscle tissue, especially when combined with exercise, as previously shown in a single bout of moderate-intensity exercise under hypoxic conditions (Mackenzie et al., 2012). In our study, participants were seated and relaxed during the intervention, which might have led to lipid rather than carbohydrate consumption (Hall et al., 2021). This is corroborated by decreases in albumin and triglycerides, indicating that the body is utilizing blood lipids more and carbohydrates less at rest (Gugliucci, 2023). One limitation of the study is that catecholamine concentrations were not assessed. However, it is likely that it would have risen to some extent, as the heart rate increased, a response contingent on catecholamines (Chatzinikolaou et al., 2008). Although catecholamines stimulate glycogenolysis and lipolysis, an increase in glycerol was not observed (it was not detectable immediately following IHNT). Concurrently, a decrease in triglycerides was observed, suggesting that the muscular system utilized them during intermittent hypoxia.

Comparison between E.T. and C.T. indicates that the acute response was driven primarily by the exercise bout itself rather than by substantial differences in internal load induced by preceding IHNT. In support of this interpretation, no between-trial differences were observed for heart-rate-derived indices, training load, or rating of perceived exertion, whereas lactate showed a similarly marked rise across the exercise cycles in both trials, with no time × trial interaction. At the metabolic level, the same comparative pattern was evident for most variables: glucose, insulin, HOMA-IR, triglycerides, albumin, and glycerol changed over time without differential trial effects, whereas only 25(OH)D and urea displayed significant time × trial interactions. Taken together, these findings indicate that, under the present protocol, preceding IHNT did not materially alter the overall acute metabolic profile of the subsequent m-HIIT session but rather affected selected recovery kinetics.

Both exercise-containing conditions were characterized by immediate post-exercise increases in glucose and insulin. Because glucose was measured only before and immediately after exercise, and not during the bout itself, the present data do not permit direct conclusions regarding intra-exercise glucose kinetics. Nevertheless, the pronounced elevation in lactate in both trials supports the interpretation that the session imposed a substantial glycolytic demand irrespective of condition. Accordingly, the post-exercise increases in glucose and insulin are more appropriately interpreted as a common early recovery response to exercise-induced carbohydrate turnover than as evidence of a trial-specific glucoregulatory effect. This interpretation is consistent with the physiology of intense intermittent exercise, during which hepatic glucose output increases and contraction-mediated glucose uptake occurs via insulin-independent mechanisms involving GLUT4 translocation (Howlett et al., 1999; Richter and Hargreaves, 2013; Trefts et al., 2015). Importantly, although C.T. incorporated prior hypoxic exposure by design, glucose and insulin did not show differential temporal behavior relative to E.T.; therefore, any contribution of IHNT to glucose regulation should be viewed as secondary to the exercise stimulus itself. Human evidence suggests that hypoxia-related exposure can modify substrate regulation under some conditions (Brooks et al., 1991), yet the present findings do not support a distinct glucoregulatory phenotype in C.T.

A similar exercise-dominant pattern was observed for glycerol. In both E.T. and C.T., glycerol increased after exercise, and no time × trial interaction was detected, indicating that lipid mobilization was activated in both conditions irrespective of preceding IHNT. This point is central because it shows that, unlike 25(OH)D and urea, glycerol did not differentiate between the two trials. The present pattern is consistent with previous work from our group showing that adipose tissue triacylglycerol lipase activity increases rapidly during moderate aerobic exercise (Petridou and Mougios, 2002) and is markedly upregulated during acute circuit resistance exercise (Chatzinikolaou et al., 2008). Particularly relevant is the circuit-resistance study, in which plasma insulin increased in the obese group while lipolytic activation remained evident, a finding that aligns closely with the coexistence of elevated insulin and glycerol in the present study. More recent work from the same research line further showed that endurance exercise can elicit different temporal patterns of lipolytic stimulation in lean and obese men (Petridou et al., 2017). Read against that body of work, the present glycerol findings support a narrow but strong conclusion: the lipolytic signal in this study was exercise-driven and common to both E.T. and C.T., rather than a selective effect of preceding IHNT. Because adipose lipolysis is regulated by both stimulatory β-adrenergic and inhibitory α2-adrenergic pathways, receptor saturation could have contributed to the lack of a differential glycerol response; however, the present data are insufficient to directly verify this mechanism. If prior IHNT altered adrenergic signaling, that effect was not large enough to translate into divergent glycerol kinetics in the present study (Lafontan and Berlan, 1993).

The comparison between glycerol and 25(OH)D sharpens that interpretation further and should be treated as a key result rather than a side note. Whereas glycerol rose similarly in both trials, 25(OH)D displayed a significant time × trial interaction, indicating that these two adipose-related variables did not behave identically. This contrast is important because it argues against a simple “greater lipolysis in one trial” interpretation. Vitamin D can reasonably be discussed within an adipose-linked framework because it is lipophilic and can be sequestered in adipose tissue, which may reduce its circulating bioavailability in obesity (Wortsman et al., 2000). In addition, exercise has been reported to transiently increase circulating vitamin D metabolites, and adipose-tissue-related turnover has been proposed as one possible contributor to that response (Davies et al., 2024; Hengist et al., 2019). The present data are broadly compatible with that framework, but they also impose an important limit on interpretation. Because glycerol did not differ temporally between E.T. and C.T., whereas 25(OH)D did, preceding IHNT appears more likely to have influenced vitamin D kinetics, transport, binding, or tissue exchange than to have altered the lipolytic response itself. Thus, the vitamin D finding should not be presented as proof of greater lipolysis in one condition; rather, it identifies a trial-specific metabolic feature superimposed on an otherwise similar exercise-induced glycerol response.

A comparable result-driven contrast was observed in the protein-related variables. Urea showed a significant time × trial interaction, whereas albumin changed over time without a differential effect across trials. Thus, as with 25(OH)D but unlike glucose, insulin, lactate, and glycerol, urea displayed trial-specific temporal behavior. That is the main finding, and it should not be diluted by broader speculation. The present data do not justify stronger claims about hepatic protein catabolism, urea-cycle suppression, or enhanced anabolism. Circulating urea reflects both hepatic production and renal handling, whereas albumin concentration is affected by exercise-induced fluid shifts and therefore cannot serve as a surrogate marker of muscle protein synthesis here. The narrowest defensible conclusion is that the preceding IHNT modified selected aspects of nitrogen-related recovery kinetics, rather than enhancing protein synthesis or broadly altering protein metabolism (Carraro et al., 1993).

Dependencies on glucose and insulin in C.T. were consistent with the exercise protocol results, demonstrating that glucose metabolism is essential under hypoxic conditions. The results suggest a hepatic postganglionic effect of catecholamines on glycogenolysis and gluconeogenesis. It is likely that acute sympathetic nervous system stimulation in the liver, as well as circulating catecholamines, could increase glucagon's effects by reducing insulin's effects (Brooks et al., 1991). Previously noted that acute hypoxia in canines was induced by ventilation with 8% O2-92% N2, which led to an increase in plasma glucagon (Baum et al., 1979). Baum et al. (1979) concluded that the glucagon response to hypoxia is mediated adrenergically, with a significant role played by the cytoreceptors, as the increase in glucagon in response to hypoxia was inhibited by phenoxybenzamine (an α-blocker). In parallel with the reduction in TG after 3h in both trials, the hypothesis of increased free fatty acid utilization in subjects acutely exposed to hypoxia was derived from a rise in plasma glycerol (Jones et al., 1972).

Conclusion

The outcomes of the present study align with recent research and substantiate the effects of acute exercise on metabolism. A single trial of IHNT activates the HIF-1a, increases HR, and reduces SpO2. Additionally, elevated glucose levels seem to lead the muscle to utilize more lipids than carbs. The results of the exercise were in complete agreement with other studies, emphasizing the stimulation of glycolysis following a single exercise session. Lastly, this was the first study to examine the metabolic adaptations to m-HIIT following an IHNT session, rather than exercise in hypoxic conditions. The results led to a variety of modifications in vitamin D levels and in the effects of catecholamines on glycogenolysis and gluconeogenesis. Further research is needed to clarify adaptations to acute IHNT and the combination of IHNT with high-intensity exercise in healthy populations.

Limitations

Several limitations should be acknowledged. FFAs, adipose tissue triacylglycerol lipase activity (TGLA), and glucagon were not measured, limiting the mechanistic interpretation of glycolysis. The small sample size and the male-only cohort, as women were excluded to avoid the impact of fluctuations in estrogen throughout the menstrual cycle on physiological responses to intermittent hypoxia, limit generalizability. Additionally, the study examined acute responses only and did not assess long-term adaptations.

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Authors´ contribution. E.M., C.A., S.I., A.A.: Conceptualization; E.M., C.A., S.I., A.A., Z.C., K.I., F.I.: Methodology; K.C., S.T., R.N.O, P.D.: Software; K.C., S.T., K.I., P.D., Z.N., F.P.: Formal analysis; C.A., S.I., A.A.; M.M., K.I., Z.N., F.P.: Validation; E.M., D.D., C.A., S.I., A.A., Z.C, P.M., F.I.: Investigation; E.M., B.D., C.A., S.I., A.A.: Writing; E.M., B.D., C.A., S.I., A.A., F.I., P.D.: Review and editing; S.T., B.D., P.M., M.M., P.D., Z.N., F.P.: Visualisation.

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