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Leukocytes and lactate responses to cycling and running at the same target heart rate

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Abstract

Heart Rate (HR) is widely used for erobic exercise intensity prescriptions and/or studies of exercise training. It is often assumed that exercising at a given HR results in similar physiological response, regardless of exercise modality. This study aimed to gauge cellular immune mobilization to submaximal exercise at a given target HR on a cycle ergometer (CE) and treadmill (TM). Thirteen healthy male adults (23.2 ± 3.5 y.o) completed 4 laboratory visits. Participants performed two graded exercise tests to exhaustion on CE and TM and two 30-min constant exercise challenges at 70% HR reserve on CE or TM in random order. Rating of Perceived Exertion (RPE) was recorded every 5 min, and blood was drawn before and after exercise to measure leukocytes subpopulation levels, lactate, and IL-6. HR was successfully "clamped" during the exercise in CE and TM (CE 156.7 ± 1.1; TM 159.3 ± 1.6 bpm). Cycling was perceived as more strenuous than running and was accompanied by a greater increase in lactate post-exercise ($p < 0.0001$; 6.2 ± 0.3 vs. 2.9 ± 0.3 mmol/L). IL-6 and leukocytes subpopulations were significantly elevated post-exercise ($p < 0.003$) with no difference between exercise modalities (monocytes; CE 57.6% TM 61.2%, granulocytes; CE 41.37%, TM 50.1%, lymphocytes; CE 91.03%, TM 78.8%). The findings revealed that HR is not sufficient in and of itself to fully assess the metabolic stress associated with a given exercise modality. However, despite different metabolic and subjective stress, the IL-6 and leukocyte counts relative changes were similar in the two modalities.

KEYWORDS
cycle ergometer, exercise, exercise prescription, modalities, submaximal exercise, treadmill, white blood cells

Highlights

- These findings provide valuable insights into the leukocytes and lactate responses to cycling and running at the same target heart rate. The study further elaborates on the shared patterns and distinctions in physiological and metabolic responses and their implications for designing targeted training programs.

- At the same target heart rate, running resulted in significantly lower lactate levels and subjective rate of perceived exertion (RPE) while yielding higher VO_2 levels compared to cycling.
- Leukocytes and IL-6 increases post-exercise were not different between running and cycling, indicating that they did not reflect the distinct metabolic and subjective perceived loads associated with cycling and running.
- Since heart rate in and of itself is not sufficient to fully characterize the metabolic stress induced by a specific exercise modality, it is important to consider the modality of exercise when prescribing training programs for improving cardiovascular fitness or achieving target energy expenditure through heart rate monitoring.

1 | INTRODUCTION

Exercise intensity affects the acute and chronic physiological responses to training. Heart Rate (HR) is widely used as a marker for exercise intensity when designing and implementing physical activity or erobic training programs, as well as in exercise research settings. The American College of Sports Medicine (ACSM) recommends exercising at 40%–85% heart rate reserve (HRR) or oxygen uptake reserve (VO_2R) to promote health in adults (Garber et al., 2011; Liguori & Medicine, 2020). For substantial health benefits, it is recommended that adults exercise for at least 150–300 min per week at moderate intensity or 75–150 min per week at vigorous intensity erobic physical activity (Bull et al., 2020). Although metabolic exercise intensity is best quantified by its oxygen cost, measurement of the latter is not always accessible. In view of the linear relationship between VO_2 and HR during exercise (Skinner et al., 2003; Wilmore & Haskell, 1971), a common approach to prescribe relative exercise intensity, in accordance with ACSM recommendations, is using a percentage of maximal heart rate (HRmax) or HRR (Mann et al., 2013).

The ACSM recommendations are focused on intensity assessed by HR and do not specify different modalities (e.g., cycling and running), despite ubiquitous findings that exercise modality affects physiological responses (Millet et al., 2009; Roecker et al., 2003). For example, in untrained individuals, the use of greater muscle mass in running has been demonstrated to result in higher HRmax and VO_2max values compared with cycling (Millet et al., 2009; Roecker et al., 2003). However, when comparing the responses to submaximal exercise intensities, set to the same percentage of maximum oxygen uptake on a treadmill (TM) and cycle ergometer (CE), higher heart rates and lactate concentrations were measured on the CE (Hermanse & Saltin, 1969; Hermansen et al., 1970), indicating that these two exercise modalities elicit different physiological and metabolic responses. Similarly, when using subjective measures, such as the rate of perceived exertion (RPE), to prescribe or monitor exercise intensity, higher HR is reported during running compared with cycling (Hassmen, 1990). Thus, while the ACSM's recommendation to exercise at 40%–85% of HRR appears straightforward, the ensuing physiological response at any given HRR may depend on the exercise modality.

In the past 2 decades, the immune response to exercise has been the subject of much research as it provides an opportunity to investigate basic adaptations to exercise and training and may have clinical implications (Pedersen & Hoffman-Goetz, 2000). The acute cellular immune response to exercise is marked by changes in the various subtypes of immune cells with an exercise-induced increase in leukocytes being the most commonly described response (Eliakim et al., 1997; Schlagheck et al., 2020). Exercise triggers a temporary increase in leukocyte levels, particularly neutrophils and lymphocytes, which are essential components of the immune system and help mobilize immune cells to potential sites of damage or infection. This exercise-induced leukocytosis is linked to the release of proinflammatory cytokines, such as interleukin-6 (IL-6), which play a role in regulating the inflammatory response to exercise and contribute to tissue repair and adaptation (Febbraio & Pedersen, 2002; Rogeri et al., 2020). As is the case with HR, immune cell mobilization and inflammatory response may also be dependent on exercise modality (Schlagheck et al., 2020). However, the effect of exercise modality (CE vs. TM) at the same target heart rate on the immune system and specifically on the leukocytes response has not been examined.

This study aimed to gauge and compare the metabolic response (oxygen uptake and lactate levels), leukocytes count, and interleukin-6 (IL-6) levels, as well as the perceived response (RPE) to submaximal exercise at a given target HR while cycling (on CE) versus running (on TM). In accordance with ACSM's recommendations, calculated target HR was based on the highest measured HR (HRmax) and lowest measured resting HR (HRrest).

2 | MATERIALS AND METHODS

The study was cleared by the Institutional Review Board of the University of California, Irvine. Following a detailed explanation of the study's tests and procedures, written informed consent was obtained from all participants.

2.1 | Participants

Thirteen healthy young male adults (23.2 ± 3.5 years; height = 175.3 ± 6.9 cm; body mass = 78.3 ± 9.1 kg; BMI 25.5 ± 0.7 kg/m^2, %fat 19.4 ± 6.3) participated in the study. Participants habitually took part in various forms of physical activity

(e.g., hiking, basketball, and strength training), but none were considered cyclists or runners. No participant had any evidence of disease or disability that would impair exercise performance. Exclusion criteria were as follows: competitive athletes, obesity, >35 years/old, and individuals with a history of any chronic medical conditions or medication use.

2.2 | Study procedures

All participants completed four exercise sessions, within 30 days, in the UC Irvine Pediatric Exercise and Genomics Research Center's Human Performance Laboratory. During the first 2 sessions, participants performed maximal cardiopulmonary exercise tests (CPETs) with ramp-type protocol on a cycle ergometer (Lode Excalibur Sport Ergometer, Netherlands) or on a treadmill (Full Vision Trackmaster TMX428CP, Newton, Kansas, USA) in a random order. Those visits were performed at least 48 h apart and not more than 9 days apart. During sessions 3 and 4, participants completed a 30-min constant submaximal exercise challenge at 70% HRR on CE or TM in a random order. Blood samples were collected before and immediately after the 30-min exercise challenge for the measurement of lactate and IL-6 levels and leukocytes count.

2.3 | Maximal cardiopulmonary exercise test-CPET

Prior to the Cardiopulmonary Exercise test (CPET), participants rested on a recliner chair for 15 min and resting HR (average of last minute) was recorded. Each CPET lasted 8–12 min until the limit of the participant's tolerance. Peak VO_2 and peak HR were determined as the highest value calculated over 20 s (rolling average) in the last 2 min of the CPET. HR was measured using Polar H10 HR monitor, while oxygen uptake was measured breath-by breath using the SensorMedics metabolic system (V_{max} 229, Yorba Linda, CA).

On the CE, participants first sat comfortably without pedaling ("resting") for 3 min and then began unloaded warm-up pedaling for 1 min, followed by incremental increases in the work rate at a rate of 20–30 W/min until exhaustion. Participants were asked to maintain a pedal cadence of 70–80 revolutions per minute (rpm). The test was terminated when the participant could no longer maintain a cadence of 60 rpm despite encouragement by the investigators. On the TM, participants initially walked at 1.5% incline, at a self-selected comfortable speed for 3 min (warm-up), followed by an increase of 1 km/h every min until they reached a comfortable running speed. Subsequently, the incline was increased by 1% every minute. The test was terminated when the participant could no longer maintain the running intensity.

2.4 | Constant submaximal exercise

On visits 3 and 4, participants completed a 30-min constant submaximal exercise challenge at 70% HRR on CE or TM. Participants were asked to refrain from intense exercise 24 h before their exercise challenge days and to arrive in a fasted state. Target HR was calculated using the Karvonen formula $HR_{rest} + 0.7(HR_{max} - HR_{rest})$ (Karvonen et al., 1957). HR_{rest} was the lowest HR value recorded in either of the two prior laboratory visits. For all participants, the highest peak HR in CPET was achieved on the TM and was used as HRmax for this calculation. HR was continuously monitored during exercise using Polar heart rate monitor. During the 30-min exercise, the HR at the last 10 s of every 5 min was recorded (6 time points). Breath-by-breath gas exchange parameters were measured on a subgroup of participants ($n = 5$) between 10 and 15 min and 25 and 30 min during both CE and TM constant load exercise sessions. In addition, participants rated their perceived effort using Borg's Rating of Perceived Exertion (RPE) scale of 6–20, every 5 min during the 30-min exercise challenges immediately after recording the HR.

2.5 | Leukocytes, lactate, and IL-6 measurements

Complete Blood Count with differential (CBCWID) test was performed in the UC Irvine pathology clinical laboratory. This test (CBCWID) provides the results of total white blood cell count (leukocytes) as well as count of different leukocyte subtypes (neutrophils, lymphocytes, and monocytes). EDTA blood was collected from participants before exercise (baseline) and immediately after exercise. ~1 ml EDTA blood was sent to the clinical laboratory to run CBCWID. The remaining volume was used to obtain plasma for Lactate and IL-6 analyses. CBC was determined utilizing the Beckman Coulter DXH900 analyzer. White blood cell differentiation was carried out via flow cytometry after erythrolysis and applying a fixative to the blood to preserve the internal structure of the cells. With this method, each cell is differentiated based on its volume (size) conductivity, which checks the granularity and light scatter as each cell goes through a flow cell with 5 different angles. To separate the plasma, blood was centrifuged at 1500xg for 15 min and aliquoted and stored at −80°C for subsequent analyses. Plasma lactate concentration was measured using YSI 2300 STAT Plus Glucose and Lactate Analyzer. IL-6 plasma concentration was determined using a colorimeteric enzyme-linked immunosorbent assay (ELISA), following the manufacturer's protocol for quantitative detection of human IL-6. IL-6 high sensitivity ELISA kit (Invitrogen Thermofisher cat# BMS213HS) with a sensitivity of 0.03 pg/ml and a standard detection range from 0.08 to 5 pg/ml was used. All samples were run in duplicates. Intra-assay variability was 4.9%, whereas the interassay variability was 6.0%. One participant had IL-6 values above the upper limit of the assay across all timepoints and hence excluded from this analysis.

2.6 | Statistical analysis

All statistical analyses were performed using SAS 9.4. The normality assessment for each marker's distribution was performed using the

Shapiro–Wilk and Kolmogorov–Smirnov tests confirming normality. Repeated measures mixed models analyses evaluating the effect of modality (CE vs. TM), assessment point (pre and post), and modality-by-assessment point interaction was used for lactate, neutrophils, monocytes, lymphocytes, and IL6. Paired *t*-test was used to evaluate within-person differences between TM versus CE for mean sub-maximal exercise HR and mean VO_2.

Repeated measures mixed model was used for RPE analysis, evaluating the effect of modality (CE vs. TM), time (5 intervals), and modality-by-time interaction. For RPE mixed models analyses, the two factors were both specified as repeated factors (i.e., within person). Post hoc analyses were performed using Tukey corrections for paired comparisons.

3 | RESULT

Table 1 displays the results of the peak and submaximal HR and VO_2 during the exercise tests. $HR_{rest,}$ lowest value recorded in either of the two prior laboratory visits was 57.9 ± 5.8 beats per minute. Both peak HR ($t = 6.028$, df = 12, and $p < 0.0001$) and peak VO_2 ($t = 9.693$, df = 12, and $p < 0.0001$) were significantly higher during running compared to cycling. Throughout both submaximal exercise sessions (CE and TM), HR was successfully "clamped" (Figure 1). Thus, at submaximal exercise, while maintaining the same heart rate, VO_2 was significantly higher ($t = 4.270$, df = 9, and $p = 0.002$) during running on TM.

Participants perceived the CE challenge as more strenuous than the TM (modality main effect: $F_{1,12} = 7.30$; $p = 0.019$.; 12.8 ± 0.4 vs. 11.6 ± 0.3, respectively) with no time or time-by-modality interaction (Figure 1). The largest differences were seen in the first 10 min with large effect sizes seen at both 5-min ($d = 1.85$) and 10-min ($d = 1.27$) ratings.

There were no significant differences in resting lactate between CE and TM. Repeated measures mixed model results revealed a significant modality by time interaction ($F_{1,11}$) = 243.06, $p < 0.0001$), indicating that while there was a substantial increase in lactate levels post-exercise in both modalities (Pre-Post CE: $t = 8.8$, $p < 0.001$; Pre-Post TM: $t = 4.6$, $p = 0.0008$), the change in lactate levels (post -pre-exercise) was significantly greater following CE (4.4 ± 1.7 mmol/L) than following TM (1.4 ± 1.0 mmol/L; $t = 5.21$, $p = 0.0003$) (Figure 2).

Leukocytes were significantly elevated ($F_{1,11} = 26.64$; $p < 0.0003$) immediately after both CE and TM sessions across all subgroups: neutrophils ($F_{1,11} = 52.95$; $p < 0.0001$); monocytes ($F_{1,11} = 30.91$; $p < 0.0002$); and lymphocytes ($F_{1,11} = 43.03$; $p < 0.0001$) (Figure 3) with no significant difference between exercise modalities. IL-6 levels significantly increased ($F_{1,18} = 10.8$; $p = 0.004$) immediately post-running and cycling (21.1 ± 18.3% and 16.0 ± 17.1%, respectively) with no significant difference between exercise modalities (Figure 4).

TABLE 1 Physiological responses to cycling and running exercise at maximal and submaximal intensities (mean ± SD).

	Cycle	Treadmill
Maximal exercise		
Peak VO_2 (ml/kg/min)[a]	44.2 ± 8.2	52.0 ± 8.0
Peak HR (bpm)[a]	187 ± 10.7	199 ± 10.6
Submaximal exercise		
[b]VO_2 (ml/kg/min)[a]	29.34 ± 8.3	34.18 ± 9.1
HR (bpm)	156.7 ± 1.0	159.3 ± 1.6

Abbreviations: VO_2, oxygen consumption; HR, heart rate.

[a]Reflects significant difference between modalities, $p < 0.01$.

[b]VO_2 (ml/kg/min) was measured on a subgroup of participants ($n = 5$) between 10–15 min and 25–30 min.

4 | DISCUSSION

We examined the metabolic, leukocytes count, and IL-6 levels to submaximal exercise at the same target heart rate using different exercise modalities (i.e., CE and TM) among healthy young men. The findings demonstrate that running at 70% of heart rate reserve (HRR) resulted in a higher oxygen uptake, lower lactate, and lower rate of perceived exertion compared with cycling. On the other hand, the elevations in leukocytes count and IL-6 levels were similar regardless of the exercise modality. The differential metabolic response may have implications for exercise prescription, specifically when fitness or energy expenditure may be of interest (e.g., weight management and recreational cardiovascular fitness). That is, when metabolic and subjective responses are of interest, exercise modality should be taken into consideration. In relation to leukocyte count and IL-6 levels, our findings do not indicate a difference between the two modalities.

Due to the accessibility of HR measurements (e.g., HR monitors and smart watches), a common approach to exercise prescription involves the determination of a target HR. Target HR is often calculated based on the estimation of maximum HR using a formula such as 220-age (FOX III, 1971). In the present study, we used a direct measurement to determine each individual's highest HR on both CT and TM. In all cases, the highest value was attained during running and was used to calculate the target HR. Therefore, participants exercised at the same HR in both cycling and running modalities. Such an approach provides context validity to our study design.

While the most commonly used approach to exercise intensity prescription is using relative HR, previous research comparing between exercise modalities has also used metabolic indicators (e.g., % VO_2max) to determine exercise intensity with inconsistent findings. For example, some studies report that at a similar %VO_2max, fat oxidation was higher while HR and lactate concentrations were lower during running compared with cycling (Scharhag-Rosenberger et al., 2010). Others report lower lactate concentrations but higher

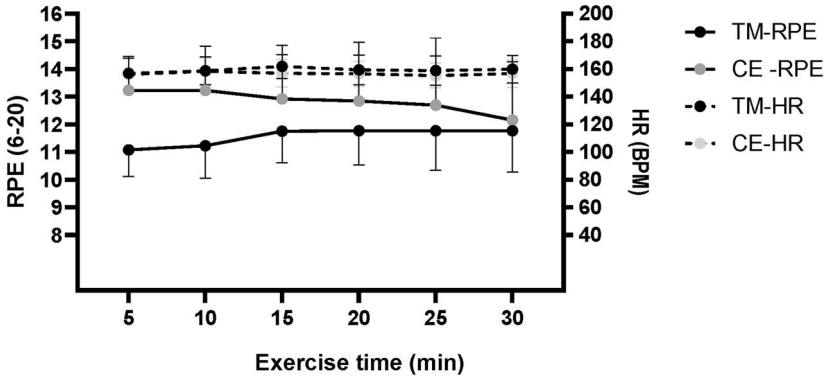

FIGURE 1 Rate of perceived exertion (RPE) (solid lines) and Heart rate (HR) (brake lines) during 30 min submaximal cycling (CE, gray symbols) and treadmill running (TM, black symbols).

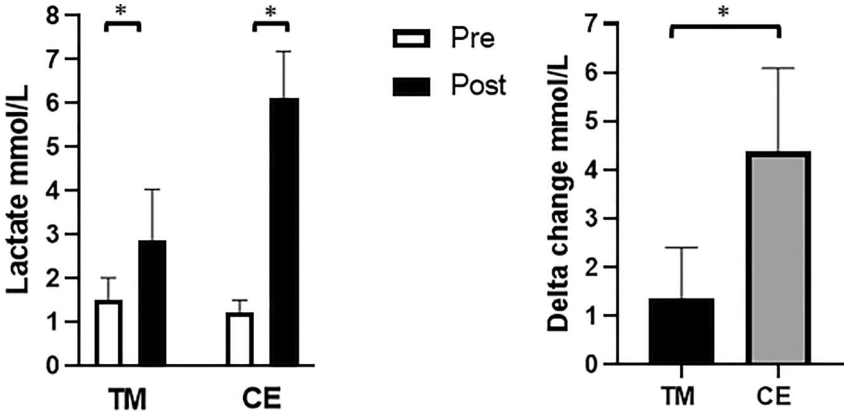

FIGURE 2 Lactate concentration (Mean ± SD) pre- and post-submaximal cycling and running. * significant difference ($p < 0.001$) between running on treadmill (TM) and cycling on cycle ergometer (CE).
[Corrections made on 16 April 2024, after first online publication: Variables 'Lactate' (left) and 'Delta change' (right) has been included in y-axiz in this version]

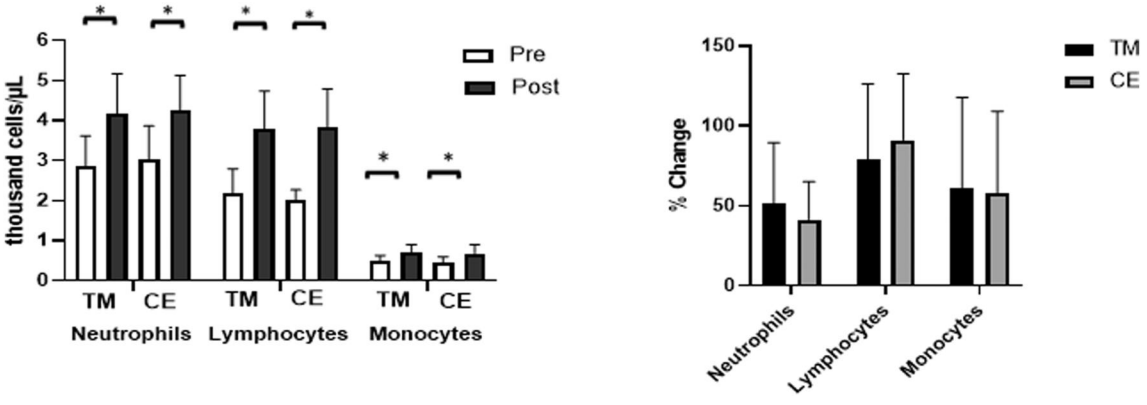

FIGURE 3 Leukocytes concentration (Mean ± SD) pre- and post-submaximal cycling (CE) and running (TM). *p = <0.01. Left panel: differences between pre (white columns) and post exercise (black column) on each modality; Right panel: delta of change (post-pre) for each modality.

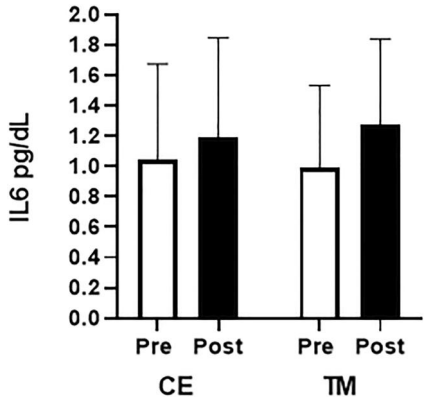

FIGURE 4 IL6 level (Mean ± SD) pre- and post-submaximal cycling (CE) and running (TM); $F_{1,18} = 10.8$; $p = 0.004$.
[Corrections made on 16 April 2024, after first online publication: Variable 'IL6' has been included in y axis in this version]

HR during running compared with cycling (Miles et al., 1980). Conversely, exercising at the same lactate concentration (4 mmol/L) resulted in lower HR during running compared with cycling (Roecker et al., 2003). In the present study, while HR was similar in the two exercise modalities, VO_2 was higher while lactate concentrations and subjective effort were lower during running.

The higher VO_2 observed during running is in agreement with previous studies (Achten et al., 2003; Lafortuna et al., 2010). For example, among obese adolescents, Lafortuna et al. (2010) reported higher energy expenditure and oxygen uptake during running compared with cycling at a comparable HR. The higher VO_2 observed during running can be attributed to the engagement of a larger muscle mass and a greater involvement of upperbody musculature, which leads to higher energy expenditure and oxygen uptake (Bijker et al., 2002).

While VO_2 was higher during running, lactate concentrations increased to a greater extent during cycling. Lafortuna et al. (2010) also reported greater lactate responses during cycling compared to running at a comparable heart rate. The authors suggested that cycling imposes greater metabolic involvement, and therefore greater lactate production at the level of individual active muscles compared to running. Along these lines, Carter et al. (2000) suggested that cycling may involve a greater utilization of type II fibers leading to higher glycolytic metabolism and subsequently a greater lactate response (Carter et al., 2000). Running involves greater eccentric muscle action and utilization of stored elastic energy and may thus rely less on the recruitment of type II motor units compared to cycling at the same relative exercise intensity. This lower use of type II motor units during running may result in lower lactate accumulation. Furthermore, the lower involvement of upper body muscles in stationary cycling may result in lower lactate breakdown by these muscles, further contributing to the higher lactate levels observed after cycling.

The perception of exertion (RPE) as an indicator of physical strain has been studied widely in different exercise modalities and protocols, as well as in various populations, and has been shown to linearly associate with HR (Borg et al., 1987). Hassmen reported that during running and cycling at the same RPE, the former resulted in higher HR, specifically among nonathletes (Hassmen, 1990). Similarly, Zeni et al. (1996) reported higher HR during treadmill running compared with cycle ergometry among women (Zeni et al., 1996). Thus, our results of lower RPE during running are consistent with previous research among similar and different populations.

Leukocytosis during and post-exercise is generally considered a normal physiological response to the stress of physical activity. It helps the body to prepare for potential injury, inflammation, or infections that might occur during or after exercise. Exercise triggers the activation of the hypothalamic–pituitary–adrenal (HPA) axis leading to an increase in cortisol levels commonly known as the stress hormone. Elevated cortisol levels, in turn, reduce adhesion molecule expression in leukocytes. This reduction allows white blood cells to move more freely into tissues contributing to exercise-induced leukocytosis (Gleeson et al., 2013). Little is known about the leukocytes response to different exercise modalities. Specifically, a single bout of high intensity erobic exercise has been shown to increase neutrophil, monocytes, and lymphocytes counts and function (Radom-Aizik et al., 2008; Shephard, 2003; Wolach et al., 2000). The current study showed that exercise at 70% of HRR for 30 min, as recommended by the American College of Sport Medicine (Ag Daud et al., 2019), led to leukocytosis independent of exercise modality. Thus, our results are in agreement with previous findings and extend the current knowledge to different modalities.

Many of the changes in the cellular immune response depend on the type of exercise (e.g., erobic vs. anaerobic (Wolach et al., 2000) and on the intensity of the exercise (Cerqueira et al., 2020; Edwards et al., 2007; Neves et al., 2015).

In the present study, one may argue that despite the similar HR, the metabolic 'intensity' as reflected by oxygen uptake and lactate response and the subjective 'intensity' as reflected by RPE were different between the two modalities. Nevertheless, these variations did not impact the leukocytosis or IL-6 response.

IL-6 is a protein and signaling molecule in the immune system, which plays a crucial role in regulating both pro and anti-inflammatory effects. IL-6 is produced by various cells, including white blood cells (Kany et al., 2019) and muscle cells (Pedersen, 2019), and is involved in both acute and chronic inflammation. IL-6 produced during exercise is thought to have anti-inflammatory effects by helping to regulate the immune response and protect against excessive inflammation (Pedersen, 2019). The response of IL-6 to exercise can vary depending on factors such as the type, intensity, and duration of exercise (Nash et al., 2023) as well as muscle mass involved (Pedersen, 2019). In the present study, despite different metabolic and subjective strains, when exercising on CE or TM at the same target HR, leukocytes counts and IL-6 response post-exercise were not different between the two exercise modalities. Yet, the modality effect on leukocyte function/immune response at this given intensity, or other intensities and durations, is unknown. Further investigations are needed to better understand the immune response to different exercise modalities and long-term training adaptations of cycling and running.

5 | CONCLUSION

When exercising at the same target HR, RPE and lactate concentration were found to be significantly lower and VO_2 higher during running compared with cycling. The leukocyte counts and IL-6 responses, however, were not different between the two modalities and did not reflect the different metabolic or subjective load. In view of the similar HR, yet different lactate and VO_2 responses, it is clear that HR is not sufficient in and of itself to characterize the metabolic stress associated with a given exercise modality. Thus, when prescribing training programs for the purpose of cardiovascular fitness or energy expenditure based on HR, it is important to consider the modality of exercise. Similarly, in research settings where the metabolic or subjective response is of interest, exercise modality should be considered. On the other hand, under the conditions of this study, when investigating the leukocyte count or IL-6 response, exercise modality does not appear to play a role. Future studies exploring omics responses (i.e., transcriptomics, proteomics, and metabolomics) may offer valuable insight into the potential mechanisms underlying immune system responses when exercising at the same target HR on different exercise modalities.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare. All coauthors have seen and agree with the contents of the manuscript and there is no financial interest to report. The authors certify that the submission is original work and is not under review at any other publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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