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Original Article

Anti-Inflammatory Potential of Continuous and High-Intensity Interval Training in Cardiac Injury: Gene Expression Changes of TNF-α and IL-6 Following Myocardial Infarction

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Abstract

Background and aims: Myocardial infarction (MI) induces chronic inflammation and cytokine overexpression. This randomized controlled experiment investigated the effects of moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT) on cardiac tumor necrosis factor-alpha (*TNF-α*) and *IL-6* gene expression in MI-induced rats.

Methods: Forty male Wistar rats were randomized into control, MI, MI + MICT, and MI + HIIT groups (10 animals per group). MI was induced by left anterior descending artery occlusion and confirmed by echocardiography. Following recovery, rats completed 8 weeks of treadmill training (MICT: 50–60% VO_2max; HIIT: 85–90% VO_2max). Finally, cardiac TNF-α and IL-6 messenger RNA levels were measured by quantitative polymerase chain reaction and analyzed using one-way ANOVA.

Results: Ejection fraction was lower in MI rats than in controls (38 ± 5% vs. 68 ± 4%, $P<0.001$). TNF-α increased in MI (2.6 ± 0.4 vs. 1.0 ± 0.2, $P<0.001$) but decreased after MICT (1.7 ± 0.3; $P=0.001$) and HIIT (1.3 ± 0.2, $P<0.001$). Moreover, IL-6 rose in MI (2.9 ± 0.5 vs. 1.0 ± 0.2, $P<0.001$) but declined after MICT (2.0 ± 0.4, $P=0.002$) and HIIT (1.8 ± 0.3, $P<0.001$). Additionally, TNF-α reduction was greater with HIIT than MICT ($\Delta=0.4$, $P=0.010$), while IL-6 changes were not significant ($P=0.180$).

Conclusion: Overall, both MICT and HIIT mitigated cardiac inflammation after MI by reducing *TNF-α* and *IL-6* gene expression, with HIIT producing a more potent anti-inflammatory effect on TNF-α. These molecular findings suggest that HIIT may offer enhanced anti-inflammatory benefits in post-MI rehabilitation strategies.

Keywords: High-intensity interval training, Continuous training, Myocardial infarction, Tumor necrosis factor-alpha, Interleukin-6

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Introduction

Cardiovascular diseases remain the leading cause of mortality worldwide, with myocardial infarction (MI) being one of the most severe manifestations. According to the Global Burden of Disease report, these disorders are responsible for nearly 18 million deaths annually, with MI substantially contributing to this burden (1, 2). This type of infection results from coronary artery occlusion, leading to ischemia, necrosis, and progressive impairments of cardiac function (3). A critical feature of post-MI pathology is persistent inflammation, which, while initially protective, exacerbates myocardial damage when sustained over time. In addition, elevated levels of pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), contribute to structural remodeling and increase the risk of heart failure (4, 5). Therefore, identifying non-invasive interventions capable of modulating post-MI inflammatory signaling at the molecular level is of significant mechanistic relevance.

According to evidence, aerobic exercise has emerged as a promising approach to modulate molecular and cellular pathways involved in post-MI inflammation. Some preclinical and clinical studies have demonstrated that regular aerobic activity attenuates inflammatory signaling by suppressing nuclear factor kappa B activation while promoting the production of anti-inflammatory cytokines, such as IL-10 (6, 7). Continuous moderate-intensity training (MICT) has been widely reported to reduce the myocardial expression of TNF-α and IL-6 following injury (8, 9). Likewise, high-intensity interval training (HIIT) has been shown to confer superior benefits for cardiovascular function and systemic inflammation compared with MICT (10). However, there are contradictory data in this regard. For example, Latino et al (11) found transient elevations in IL-6 during high-intensity exercise, and Yavari et al (12) reported heterogeneous inflammatory responses across populations, suggesting that individual and contextual factors influence the outcomes. Such discrepancies highlight the complexity of exercise-induced immune modulation.

Despite these insights, significant gaps remain. It is noteworthy that most investigations have focused on continuous aerobic exercises, while evidence for interval training in post-MI models is limited. Moreover, a limited body of research has directly compared the effects of HIIT versus MICT on *TNF-α* and *IL-6* expression in cardiac tissues (13). The dual role of IL-6 as both pro-inflammatory

and anti-inflammatory further complicates interpretation, reinforcing the need for systematic comparative studies.

Accordingly, the present study has been designed to directly compare the effects of continuous and HIIT on *TNF-α* and *IL-6* gene expression in rat myocardium after MI. Using quantitative real-time polymerase chain reaction (qRT-PCR), it has been hypothesized that both training modalities would reduce cytokine expression compared with sedentary MI controls, with HIIT eliciting greater reductions due to its higher intensity. By addressing these gaps, this study will provide mechanistic insights into exercise-induced regulation of inflammatory cytokines in the infarcted heart, which may help refine cardiac rehabilitation strategies.

Materials and Methods

This study used an experimental design to investigate the effects of MICT and HIIT on the expression of *TNF-α* and *IL-6* genes in the myocardial tissues of rats with MI in order to evaluate the anti-inflammatory potential of these exercises. Male Wistar rats aged 10–12 weeks, with an average weight of 300 ± 50 g, were obtained from the Marvdasht Laboratory Animal Breeding Center and utilized in this study. The rats were kept in transparent polycarbonate cages, with 4 rats per cage, under controlled environmental conditions, including a temperature of 22 ± 2°C, relative humidity of 50 ± 5%, and a 12-hour light/12-hour dark cycle. Moreover, standard rat chow and water were available to the animals ad libitum. In addition, all laboratory protocols were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health. Furthermore, all stages of the research were conducted under strict supervision and in accordance with ethical standards. To account for anticipated mortality from the surgical procedure and ensure equal group sizes (n = 10) for the final analysis, a total of 48 male Wistar rats were initially used in this study. The animals were randomly allocated to four groups (n = 12 each) using a computer-generated random number sequence: healthy control (Ctrl), MI control (MI), MI + continuous training (MI + MICT), and MI + interval training (MI + HIIT). From these, 36 rats (all except the healthy Ctrl group) underwent MI surgery. During the first 48 hours post-surgery, five animals were excluded due to death from surgical or anesthetic complications. Subsequently, an exclusion criterion based on the lack of MI confirmation (ejection fraction [EF] > 50% on echocardiography) was applied, resulting in the exclusion of 1 additional animal. Then, the first 10 surviving and eligible rats from each group, as per the original randomization list, were included in the final analysis, yielding 10 rats per group and a total of 40 animals in the study. It should be noted that random allocation was conducted using a computer-generated random number sequence (simple randomization with a 1:1:1:1 allocation ratio). In addition, group assignment was performed by an investigator who was not involved in training supervision or outcome assessment, thereby ensuring allocation concealment and minimizing bias.

To create an MI model, rats underwent surgical ligation of the left anterior descending coronary artery. They were anesthetized via the intraperitoneal injection of a combination of ketamine (50 mg/kg body weight) and xylazine (10 mg/kg body weight). After stabilization on the surgical table, the chest was opened through a 10-mm incision in the intercostal space between the third and fourth ribs, and the left anterior descending coronary artery was ligated with a 6–0 polypropylene suture 1–2 mm from its origin. Successful occlusion was confirmed by observing myocardial discoloration (pallor) and ST-segment elevation on the electrocardiogram. After 48 hours, echocardiography with a 10 MHz probe was performed to assess EF and fractional shortening (FS) to confirm the presence of MI. To prevent infection and alleviate pain, cefazolin (20 mg/kg) and tramadol (10 mg/kg) were administered for three days post-surgery. Next, the success of disease induction and the normality of the data were assessed. Subsequently, the results for each gene were separately presented, followed by a comparative analysis of the effects of the two training modalities. Echocardiographic results for the confirmation of MI induction are provided in Table 1.

The results demonstrated that EF and FS were significantly reduced in the MI group compared to the healthy control group [EF: $F(3, 36) = 45.62$, $P < 0.001$; FS: $F(3, 36) = 39.74$, $P < 0.001$], confirming the successful induction of MI and comparable baseline conditions across groups prior to training.

Exercise training was initiated 7 days after MI induction. This timing was selected to allow animals to recover from surgical procedures and the acute inflammatory response to infarction, thereby reducing perioperative mortality. Starting the intervention one week after MI is consistent with previous preclinical models (14) and enables exercise to be applied during the subacute remodeling phase rather than the acute necrotic phase. The continuous and HIIT groups underwent a two-week familiarization period on the treadmill, consisting of three sessions per week, each lasting 10–15 minutes at a speed of 10–15 m/min. Then, maximal aerobic capacity was determined using an incremental treadmill test to exhaustion. Considering that direct measurement of gas exchange was not performed, the maximum speed achieved in this test was used as a surrogate for maximal oxygen uptake ($VO_{2_{max}}$), and

Table 1. Echocardiographic Results for the Confirmation of MI Induction

Group	EF (%)	FS (%)
Ctrl (n = 10)	68 ± 4	34 ± 3
MI (n = 10)	38 ± 5	19 ± 2
MI + MICT (n = 10)	39 ± 4	20 ± 3
MI + HIIT (n = 10)	40 ± 5	20 ± 2

Note. Ctrl: Healthy control group; MI: Myocardial infarction; MICT: Moderate-intensity continuous training; HIIT: High-intensity interval training; EF: Ejection fraction; FS: Fractional shortening.

exercise intensities were set as a percentage of this VO_{2max} (13). The exercise protocols were conducted for 8 weeks, five days per week, at a 0° incline (14). The detailed structure, including intensities, session duration, and weekly progression, is provided in Table 2. The MI + MICT group trained at a constant speed corresponding to 50–60% of estimated VO_{2max} for the prescribed duration. In addition, the MI + HIIT group performed repeated intervals at 85–90% of estimated VO_{2max} interspersed with active recovery periods at low intensity. The total training duration was matched between groups (14). Each exercise session began and ended with a five-minute warm-up and cool-down at 40% of VO_{2max}. In the first and second weeks, the total exercise time was approximately 60 minutes, which was increased to 62 minutes in weeks three and four, 64 minutes in weeks five and six, and 66 minutes in weeks seven and eight to ensure training progression. Table 2 presents the detailed protocols for MICT and HIIT, including volume progression over the 8-week intervention.

To minimize the influence of acute exercise-induced fluctuations and capture training-induced adaptations, myocardial tissues were collected 72 hours after the last training session. The animals were euthanized via respiratory arrest induced by placement in a chamber filled with CO_2 gas. To confirm death, a secondary method [dislocation/cervical dislocation or pneumothorax induction] was also performed immediately thereafter. The myocardial tissues were then extracted. Next, the samples were washed in physiological saline and stored at -80°C for subsequent analysis.

Total RNA was extracted from myocardial tissues using a total RNA isolation reagent (Invitrogen, USA) and treated with deoxyribonuclease I. Moreover, RNA quantity and quality were confirmed using a NanoDrop spectrophotometer (Thermo Fisher Scientific), with a 260/280 ratio > 1.8. One μg of total RNA was reverse-transcribed into complementary DNA using the RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific). Additionally, the expression of *TNF-α* and *IL-6* genes was measured by qRT-PCR on an ABI Prism 7500 instrument using gene-specific primers.

Cycling conditions were initial denaturation at 95°C for 15 minutes, followed by 40 cycles of 95°C for 30 seconds, 60°C for 30 seconds, and 72°C for 30 seconds. Melting curve analysis (55–95°C) was performed to verify product specificity. PCR efficiencies were within the acceptable range (85–110%), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the reference gene. Expression levels were reported using the 2^−ΔΔCt method, and data were analyzed using the ΔΔ Ctrl method with GAPDH as the reference gene.

For qPCR reporting, primer design information, reaction efficiency, and raw quantification cycle (Cq) values were provided in accordance with the guidelines of the Minimum Information for Publication of qRT-PCR Experiments. Primer sequences and reaction characteristics are listed in Table 3. PCR efficiency for each gene was within the acceptable range (85–110%). The mean raw Cq values for all groups were

Table 2. Detailed Overview of the 8-Week Exercise Training Protocols

Training Parameter	Moderate-Intensity Continuous Training	High-Intensity Interval Training
Intensity (% of estimated VO_{2max})	50–60%	85–90% (high-intensity interval)/50–60% (active recovery)
Session frequency	5 days/week	5 days/week
Warm-up/cool-down	5 minutes at 40% of VO_{2max}	5 min at 40% of VO_{2max}
Main exercise structure	Single, continuous run at target intensity	Repeated intervals: 4-minute high-intensity bouts interspersed with 3-minute active recovery periods
Week 1-2 duration	60 minutes/session	Total session time: ~60 minutes (e.g., 6 intervals)
Week 3-4 duration	62 minutes/session	Total session time: ~62 minutes (e.g., 6 intervals)
Week 5-6 duration	64 minutes/session	Total session time: ~64 minutes (e.g., 6 intervals)
Week 7-8 duration	66 minutes/session	Total session time: ~66 minutes (e.g., 6 intervals)
Calculation of intensity	Maximal running speed: Determined for each rat via an incremental treadmill test to exhaustion VO_{2max} estimation: The maximum speed (m/min) was used as a surrogate for 100% VO_{2max}. Target speeds for training were then calculated as the corresponding percentage of this maximal speed.	

Table 3. Primer Information, Reaction Efficiency, and Raw Cq Values of the Genes

Gene	Forward Primer Sequence (5′–3′)	Reverse Primer Sequence (5′–3′)	Amplicon Length (bp)	PCR Efficiency (%)	R^2	Raw Cq (Mean ± SD)	Stability Between Groups
GAPDH	[Forward]	[Reverse]	150	98	0.994	Ctrl: 19.2 ± 0.3, MI: 19.5 ± 0.4, MI + MICT: 19.3 ± 0.3, MI + HIIT: 19.4 ± 0.4	$P = 0.68$ (NS)
IL-6	[Forward]	[Reverse]	145	91	0.991	Ctrl: 23.4 ± 0.5, MI:28.5 ± 0.7, MI + MICT: 26.7 ± 0.6, MI + HIIT: 26.0 ± 0.6	—
TNF-α	[Forward]	[Reverse]	120	96	0.992	Ctrl: 22.5 ± 0.4, MI: 27.8 ± 0.5, MI + MICT: 25.9 ± 0.6, MI + HIIT: 24.2 ± 0.5	—

Note. Ctrl: Healthy control group; MI: Myocardial infarction; MICT: Moderate-intensity continuous training; HIIT: High-intensity interval training; EF: Ejection fraction; FS: Fractional shortening; SD: Standard deviation; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha; PCR: Polymerase chain reaction; R^2: Coefficient of determination; Cq: Quantification cycle; SD: Standard deviation; NS: Not significant.

calculated, and the stability of GAPDH across groups was confirmed ($P>0.05$).

Data were analyzed using SPSS software, version 26. To test the study hypotheses, which posit that continuous and interval aerobic exercises have differential effects on the expression of *TNF-α* and *IL-6* genes in the myocardial tissues of rats with MI, a one-way analysis of variance (ANOVA) was performed, followed by Tukey's post-hoc test for pairwise comparisons between groups. Furthermore, an independent-samples t-test was utilized to directly compare the two exercise groups. Moreover, the normality of the data was assessed on the Δ Ctrl values (not the comparative delta–delta Ctrl (ΔΔ Ctrl) values) using the Shapiro-Wilk test. Given that the Δ Ctrl distribution was normal, the results have been reported as relative values (2^-ΔΔ Ctrl).

Results

Primer efficiency and mean raw Cq values are summarized in Table 3. ANOVA results revealed no significant differences in GAPDH expression between groups ($P>0.05$), supporting its suitability as a stable reference gene for normalization.

The effects of exercise training on myocardial *TNF-α* and *IL-6* gene expression are provided in Table 4. The results of the one-way ANOVA demonstrated the significant main effect of group on *TNF-α* gene expression [$F(3, 36)=25.42$, $P<0.001$, $\eta^2=0.68$]. Post hoc Tukey comparisons (Table 4) indicated that *TNF-α* expression was significantly higher in the MI group (2.6 ± 0.4) than in the control group (1.0 ± 0.2, $P<0.001$). Both exercise interventions could considerably reduce *TNF-α* expression compared to the MI group (MI + MICT: 1.7 ± 0.3, $P=0.001$; MI + HIIT: 1.3 ± 0.2, $P<0.001$). Moreover, the MI + HIIT group showed a remarkably greater reduction than the MI + MICT group [mean difference = 0.4, $t(18)=2.76$, $P=0.010$]. A bar graph of these results is displayed in Figure 1.

Based on the independent t-test, *TNF-α* expression in MI + HIIT was significantly lower than in MI + MICT ($P=0.010$), indicating that interval training was more effective at reducing inflammation.

The one-way ANOVA confirmed a significant effect of group on *IL-6* gene expression [$F(3, 36)=21.73$,

Table 4. Effects of Exercise Training on Myocardial *TNF-α* and *IL-6* Gene Expression (Means ± SD) and Tukey's HSD Pairwise *P*-Values

Gene	Group	Mean (Relative Units) ± SD	Tukey (vs. MI) *P* Value	Tukey (MI + HIIT vs. MI + MICT) *P* Value	Mean Difference (HIIT vs. MICT) [95% CI]
TNF-α	Ctrl (n = 10)	1.0 ± 0.2	0.0003	—	—
	MI (n = 10)	2.6 ± 0.4	—	—	—
	MI + MICT (n = 10)	1.7 ± 0.3	0.0004	—	0.4 [0.1 to 0.7]
	MI + HIIT (n = 10)	1.3 ± 0.2	0.0002	0.0210	—
IL-6	Ctrl (n = 10)	1.0 ± 0.2	0.0001	—	—
	MI (n = 10)	2.9 ± 0.5	—	—	—
	MI + MICT (n = 10)	2.0 ± 0.4	0.0003	—	0.2 [-0.1 to 0.5]
	MI + HIIT (n = 10)	1.8 ± 0.3	0.0002	0.7589	—

Note. SD: Standard deviation; HSD: Honestly significant difference; ANOVA: Analysis of variance; HIIT: High-intensity interval training; TNF-α: Tumor necrosis factor-alpha; IL: Interleukin. Values are means ± SD. Pairwise comparisons were performed using Tukey's HSD post-hoc test after one-way ANOVA (α = 0.05). Reported Tukey *P*-values are shown for comparisons between each group and the MI group and for the direct comparison MI + HIIT vs. MI + MICT. CI: Confidence interval.

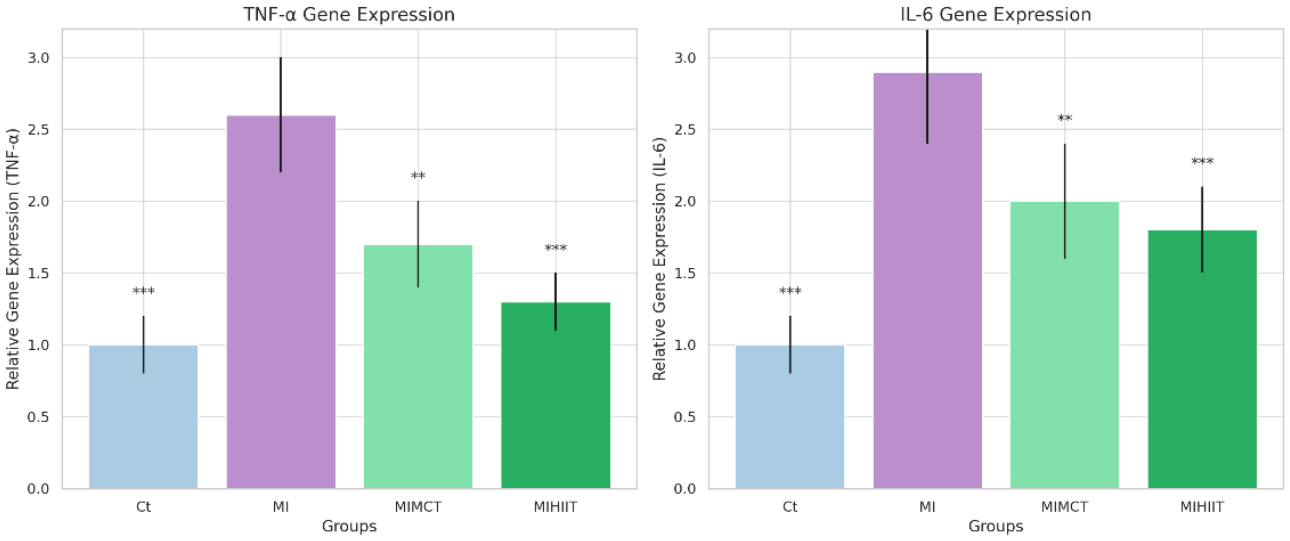

Figure 1. Visual Representation of *TNF-α* and IL-6 Gene Expression Levels in the Studied Groups
Note. TNF-α: Tumor necrosis factor-alpha; IL: Interleukin

$P<0.001$, $\eta^2=0.64$]. Post hoc Tukey analysis indicated that *IL-6* expression was noticeably higher in the MI group (2.9 ± 0.5) than in the control group (1.0 ± 0.2; $P<0.001$). Both training protocols significantly decreased *IL-6* expression (MI + MICT: 2.0 ± 0.4, $P=0.002$ and MI + HIIT: 1.8 ± 0.3, $P<0.001$). However, the difference between the two training groups was not statistically significant [t (18) = 1.37, $P=0.180$], implying similar anti-inflammatory effects on IL-6.

Discussion

This study investigated the effects of MICT and HIIT on the expression of *TNF-α* and *IL-6* genes in myocardial tissues following MI. Considering that post-infarction inflammation contributes to adverse cardiac remodeling and progression toward heart failure, it is clinically essential to identify effective non-pharmacological strategies in order to control inflammation. It was, therefore, hypothesized that both training modalities would downregulate inflammatory gene expression in myocardial tissues, with HIIT providing greater benefits due to its higher physiological load.

The significant increase in *TNF-α* expression observed in the MI group is consistent with previous studies, demonstrating *TNF-α*'s involvement in apoptosis, extracellular matrix degradation, and fibrosis in cardiac tissues (15). Both MICT and HIIT significantly reduced *TNF-α* expression, with the more pronounced decline following HIIT (approximately 50% versus 35% with MICT). This superior effect of HIIT aligns with studies indicating that higher-intensity exercise elicits stronger anti-inflammatory responses and improves cardiac metabolic efficiency more effectively than lower intensities (15, 16). One plausible explanation is that HIIT promotes greater activation of intracellular signaling pathways involved in inflammation regulation, including the suppression of nuclear factor kappa B activity (4) and the stimulation of anti-inflammatory cytokines, including IL-10 (17). Additionally, the intermittent pattern of HIIT has been shown to enhance mitochondrial biogenesis, oxidative phosphorylation, and endothelial nitric oxide production, thereby contributing to improved myocardial resilience and a reduced inflammatory burden.

In contrast, although IL-6 levels were also elevated following MI, both exercise modalities produced a statistically similar reduction in *IL-6* expression. This finding reflects the dual nature of IL-6, which acts as both a pro-inflammatory and an anti-inflammatory mediator. While acute exercise can transiently increase IL-6 release from skeletal muscle (18), chronic training adaptations typically suppress baseline *IL-6* expression by improving metabolic status while reducing visceral-derived inflammation (19). The fact that tissue sampling occurred 72 hours after the last training session suggests that the observed IL-6 changes reflect chronic biochemical adaptation rather than acute exercise-induced cytokine release. Previous research also reported variability in IL-6 responses depending on the intensity, duration, and metabolic stress of the exercise stimulus (20), which may help explain the similar effects of HIIT and MICT observed in our study.

Despite the beneficial molecular effects found in this study, no significant improvement was observed in cardiac systolic functions (EF and FS) during the 8-week intervention period. Molecular remodeling typically precedes structural and functional recovery; therefore, a longer training duration or multi-modal rehabilitation approach, combining exercise with pharmacological therapy or nutrition, may be necessary to translate gene-expression improvements into measurable cardiac performance gains.

This study had some limitations, including the use of only male rats, the lack of a sham-operated control group, and the estimation of exercise intensity based on maximal running speed rather than direct measurement of VO_2. Thus, future studies should incorporate more extended follow-up periods and evaluate additional pathways, including oxidative stress markers, mitochondrial regulatory proteins, and circulating inflammatory cytokines.

Conclusion

In general, both MICT and HIIT effectively reduced myocardial *TNF-α* and *IL-6* expression at the molecular level following MI. The decline in TNF-α was more pronounced in the HIIT group. The results demonstrated that structured aerobic exercise, particularly HIIT, may serve as an effective strategy to attenuate post-infarction inflammation. Further studies are warranted to determine whether this anti-inflammatory effect translates into improved cardiac function over a more extended period.

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Authors' Contribution

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Competing Interests

The authors declare there is no conflict of interests in the study.

Ethical Approval

The study protocol was approved by the Ethics Committee of Najafabad University (ethical code IR.IAU.NAJAFABAD.REC.1404.083).

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