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Evaluation of the Effect of Continuous and Interval Aerobic Training on Survivin Gene Expression and Cytochrome C in Myocardial Tissue of Rats Modeled with Myocardial Infarction

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A B S T R A C T

This study aimed to investigate the effects of moderate-intensity continuous training (MICT) and high-intensity interval training (MIHIIT) on Survivin gene expression and Cytochrome C levels in myocardial tissue of rats modeled with myocardial infarction. In this experimental study, 30 adult male Wistar rats (10–12 weeks, 275 ± 25 g) were assigned to five groups: healthy control, sham, myocardial infarction (MI), MICT, and MIHIIT. The MI model was induced through left anterior descending coronary artery occlusion and confirmed by echocardiography. Training protocols were performed for 8 weeks, five sessions per week. The MICT group performed continuous running at moderate intensity (15–23 m/min, 50 minutes), while the MIHIIT group completed interval running consisting of 7 sets of high-intensity bouts (20–28 m/min, 4 minutes) with active recovery periods (11–17 m/min, 3 minutes). Survivin gene expression was measured using RT-qPCR, and Cytochrome C levels were quantified using ELISA. Data were analyzed using MANOVA, ANOVA, and Tukey post-hoc tests. Myocardial infarction caused a significant increase in Cytochrome C levels and a reduction in Survivin expression compared to the healthy and sham groups ($p < .001$). Both types of aerobic training significantly reversed the infarction-induced alterations; Cytochrome C levels were reduced, and Survivin expression returned to levels comparable to the control group. When comparing the two protocols, interval training (MIHIIT) produced a greater increase in Survivin expression ($p \approx .046$), while both exercise types demonstrated similar effects on reducing Cytochrome C. Both continuous and interval aerobic training restore the survival/death balance in myocardial tissue following infarction by reducing oxidative stress and enhancing Survivin expression. These findings reinforce the role of aerobic exercise as an effective non-pharmacological intervention in cardiac rehabilitation.

Keywords: *Myocardial infarction, aerobic training, Survivin, Cytochrome C, oxidative stress*

1. Introduction

Cardiovascular diseases—particularly myocardial infarction—continue to represent one of the leading global causes of mortality and are responsible for approximately 17.9 million deaths annually according to the World Health Organization. Myocardial infarction results from acute coronary artery occlusion, leading to ischemia, oxidative stress, and cardiomyocyte apoptosis, which collectively impair cardiac function and increase the risk of heart failure (1). Given the substantial global burden of myocardial infarction, non-pharmacological interventions such as aerobic exercise play a vital role in secondary prevention and cardiac rehabilitation. Both moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT) have demonstrated promising benefits for cardiovascular health; however, their underlying molecular mechanisms—particularly regarding modulation of oxidative stress and apoptosis—require deeper investigation to optimize therapeutic strategies (2).

Apoptosis, a highly regulated form of programmed cell death, plays a central mechanistic role in myocardial injury following infarction. The *Survivin* gene, coding for a member of the inhibitor of apoptosis (IAP) protein family, promotes cellular survival by suppressing caspase activation and is a key mediator of anti-apoptotic signaling pathways (3). Conversely, Cytochrome C, normally functioning within the mitochondrial respiratory chain, is released into the cytosol during mitochondrial damage and elevated oxidative stress, subsequently activating apoptotic complexes and amplifying cardiomyocyte death (4). These two molecules serve as critical representatives of opposing survival–death signaling pathways, and changes in their expression levels sensitively reflect the pathophysiological state of post-infarction myocardium. Aerobic training—both continuous and interval—has been shown to enhance antioxidant capacity and modulate these apoptotic markers, thereby reducing myocardial apoptosis (5, 6).

Despite substantial advances in understanding apoptotic and oxidative stress pathways in myocardial infarction, important gaps remain in optimizing exercise-based interventions. The distinct effects of continuous versus interval aerobic training on *Survivin* expression and Cytochrome C levels—particularly in post-infarct myocardial tissue—have not been fully clarified. Much of the existing literature has focused on either continuous training or high-intensity interval training independently, with limited direct molecular comparisons (7). Furthermore, contradictory findings exist regarding the role of oxidative stress in exercise adaptation, especially concerning the potential for excessive ROS production during high-intensity exercise, which could offset cardioprotective effects (8). These uncertainties highlight the need for comparative studies to identify optimal exercise modalities for enhancing myocardial recovery after infarction.

Previous investigations provide evidence that aerobic exercise reduces apoptosis and oxidative stress following myocardial infarction. Continuous aerobic training has been shown to increase antioxidant enzyme activity and improve myocardial tissue resilience in infarcted animal models (5). Similarly, beneficial effects of interval training have been demonstrated, with HIIT reducing apoptosis and improving cardiac performance through modulation of regulatory molecules involved in cell survival pathways (2). Nevertheless, some studies report that interval training does not consistently outperform continuous training in reducing oxidative stress or inflammation (9). Meanwhile, research on diabetic and ischemic models suggests that continuous training combined with pharmacological agents can attenuate pro-apoptotic pathways, though such findings may not fully generalize to infarction models (6). Moreover, concerns have been raised regarding the possibility that high training intensities may elevate ROS production and exacerbate apoptosis under certain conditions (10). These inconsistencies reinforce the importance of standardized protocols and comparative experimental designs (11).

This study provides an innovative comparative analysis of continuous and interval aerobic exercise on *Survivin* gene expression and Cytochrome C levels in myocardial tissue of infarcted rats, addressing a crucial gap in the literature. In contrast to previous research that typically focused on a single exercise modality or combined exercise with pharmacological interventions, the present investigation directly evaluates both approaches to elucidate their differential molecular impacts. The significance of this study lies in its potential to resolve inconsistencies regarding exercise intensity and to provide evidence-based guidance for optimizing cardiac rehabilitation protocols (12, 13). The findings may have substantial implications for clinical

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decision-making and public health policy. By clarifying the molecular effects of continuous and interval aerobic exercise on *Survivin* and Cytochrome C, this study supports the development of targeted exercise prescriptions for patients recovering from myocardial infarction, enhancing myocardial repair and reducing the risk of secondary cardiovascular events. Continuous training, which is feasible for a broad patient population, and interval training, which offers time-efficient benefits, may both be optimized based on the insights gained from this research (14, 15). Furthermore, the findings may inform policies promoting community-based exercise interventions and contribute to reducing the global cardiovascular disease burden.

Therefore, the aim of this study is to investigate the effects of continuous and interval aerobic training on *Survivin* gene expression and Cytochrome C levels in the myocardial tissue of rats with experimentally induced myocardial infarction.

2. Methods and Materials

This study was applied in nature and conducted experimentally and laboratory-based. In this investigation, 30 adult male Wistar rats (10–12 weeks old, 275 ± 25 g) were obtained from the Marvdasht Laboratory Animal Breeding Center. The animals were housed in polycarbonate cages at a density of three rats per cage under controlled environmental conditions (temperature 22 ± 2 °C, humidity 65 ± 5%, and a 12 h light/12 h dark cycle) and had free access to standard rat chow and water. The sample size was determined based on the computational method of (16). Among the 30 rats, 18 underwent surgical left anterior descending (LAD) coronary artery ligation. Confirmation of myocardial infarction (MI) was performed using echocardiography by assessing parameters such as ejection fraction and fractional shortening. Subsequently, the rats were randomly assigned to five equal groups:

1. Healthy control group (Ct) – no intervention
2. Myocardial infarction group without training (OLAD)
3. Moderate-intensity continuous aerobic training group (MICT)
4. Moderate-intensity high-intensity interval training group (MIHIIT)
5. Sham surgical control group (Sham) – surgery without coronary ligation

All experimental procedures were approved by the university ethics committee and conducted in accordance with laboratory animal care guidelines.

To induce the MI model, rats were anesthetized using ketamine (50 mg/kg) and xylazine (10 mg/kg). After thoracotomy between the third and fourth intercostal spaces, the left anterior descending (LAD) coronary artery, identifiable along the anterior wall of the left ventricle, was ligated using a 0.6-mm polypropylene suture approximately 1–2 mm below the left atrial appendage. Indicators such as sudden discoloration of the myocardial region and ST-segment elevation on the electrocardiogram confirmed successful infarction. The thoracic layers were then sutured, and rats were disconnected from the ventilator after regaining consciousness. To manage pain and prevent infection, tramadol and cefazolin were administered twice daily, starting one day before surgery and continuing until three days postoperatively. The Sham group underwent the same surgical procedure without LAD ligation.

After a one-week recovery period, rats in the MICT and MIHIIT groups entered the training phase. Initially, for two weeks (three sessions per week, 10–15 minutes per session), rats were familiarized with the animal treadmill. To determine aerobic capacity, an incremental running test was performed. After 5 minutes of warm-up at 6 m/min, the treadmill speed increased by 1.8–2 m/min every two minutes until the rats reached exhaustion (17). The mean time and speed obtained from this test were used to design the training protocols.

Training sessions were performed for 8 weeks, five times per week, at 0% incline. In the MICT group (continuous training), each session included 5 minutes of warm-up (40% VO_2max), 50 minutes of moderate-intensity running (15–23 m/min), and 5 minutes of cool-down (40% VO_2max). In contrast, the MIHIIT protocol (interval training) included 5 minutes of warm-up (40% VO_2max), 7 sets of high-intensity running (20–28 m/min, 4 minutes each) with active recovery intervals between sets (11–17 m/min, 3 minutes), followed by 5 minutes of cool-down. This design was based on the protocols of (18, 19).

Seventy-two hours after the final training session in week eight, animals were anesthetized with CO_2 gas. Cardiac

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blood sampling was performed, and myocardial tissue was excised, rinsed with physiological saline, and immediately frozen in RNase-free microtubes at −80 °C.

Cytochrome C levels in heart tissue lysates were measured using an ELISA kit (ZellBio GmbH, Germany), and results were reported as relative values. RNA extraction from myocardial tissue was performed using TRIzol reagent (Invitrogen, USA). RNA purity was verified using the A260/A280 ratio. cDNA synthesis was conducted using the RevertAid First Strand kit (Thermo Scientific). *Survivin* and the reference gene *Gapdh* were quantified using specific primers (SinaClon, Iran) on an ABI Prism 7500 system with Real-Time PCR. The PCR procedure included initial denaturation at 95 °C (15 minutes), followed by 40 cycles. Data analysis was performed using the ΔΔCt method.

Table 1

Primers

Source	Annealing Temp (°C)	Product Size (bp)	Primer Sequence	Gene
(20)	60	120	FW: 5′-GACCACCGCATCTCTACATTCA-3′ RV: 5′-GCTCTTGATCTGGGAGCTC-3′	*Survivin*
	55	600	FW: 5′-GCCAAGGTCATCCATGACAAC-3′ RV: 5′-GTCCACCACCCTGTTGCTGTA-3′	*Gapdh*

Data analysis was performed using SPSS version 27. To examine the effects of aerobic training on *Survivin* gene expression and Cytochrome C protein levels, multivariate analysis of variance (MANOVA) was applied. If significant effects appeared, ANOVA was performed separately for each variable, followed by Tukey HSD post-hoc tests for between-group comparisons. Statistical assumptions—including normality of distribution (Shapiro–Wilk), homogeneity of variances (Levene's test), and homogeneity of covariance matrices (Box's M test)—were assessed and confirmed. The significance level was set at 0.05.

All biochemical and molecular experiments were performed in at least three independent replicates. Environmental conditions and animal health were regularly monitored. Equipment was calibrated before use, and high-quality kits and reagents from reputable suppliers such as Qiagen and Thermo Fisher were employed. All procedures followed standard laboratory operating protocols (SOP).

3. Findings and Results

In the first step, the statistical assumptions related to data analysis were evaluated to ensure the validity of the results. The Shapiro–Wilk test indicated that the data distribution met the required normality. Similarly, Levene's test demonstrated homogeneity of variances among the study groups, and Box's M test confirmed homogeneity of covariance matrices. Based on these results, the dataset satisfied all prerequisites for multivariate analysis of variance (MANOVA), providing an appropriate basis for examining the effects of continuous and interval aerobic training on molecular and biochemical indices.

To examine the effect of the groups (Ct, Sham, MI, MICT, MIHIIT) on the variables Survivin and Cytochrome C, MANOVA was applied. These results are presented in Table 2.

Table 2

Summary of MANOVA for Dependent Variables

Test Statistic	Value	df (effect)	df (error)	F	Sig. (p)	Partial η^2
Pillai's Trace	0.731	16	92	5.421	0.000	0.486
Wilks' Lambda	0.312	16	90	5.872	0.000	0.502
Hotelling's Trace	1.942	16	88	6.013	0.000	0.507
Roy's Largest Root	1.327	4	23	7.154	0.000	0.555

As shown in Table 2, the effect of "group" on the combined dependent variables was statistically significant (Wilks' Lambda = 0.312, $p < 0.001$). This indicates that the type of intervention (no training, continuous training, or interval training) simultaneously produced significant changes in Survivin expression and the oxidative stress

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index Cytochrome C. Moreover, a Partial η^2 of approximately 0.50 indicates a large effect size; in other words, about 50% of the variation observed in the dependent variables can be attributed to group differences. This finding suggests that aerobic training (both continuous and interval) plays a substantial role in improving the balance between apoptosis and survival in myocardial tissue following infarction.

To examine the effects of the different groups on Survivin gene expression and Cytochrome C levels (reported as relative values), the means and standard deviations were first calculated. MANOVA was then performed to compare the two dependent variables simultaneously, and following its significance, univariate ANOVAs and Tukey post-hoc comparisons were conducted. The results are provided in Table 3.

Table 3

Mean ± SD of Survivin Gene Expression and Cytochrome C Levels and Statistical Test Results Across Groups

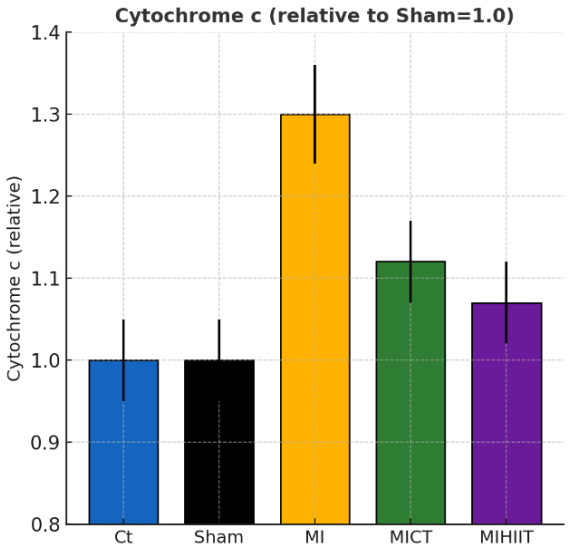
Group	Survivin (Fold vs Ct = 1.0)	Cytochrome C (relative)	ANOVA Survivin (F = 28.4, p < 0.001)	ANOVA Cyt-c (F = 18.7, p < 0.001)	Tukey Post-hoc Comparison
Ct	1.00 ± 0.05	1.00 ± 0.05	–	–	MI > Ct***
Sham	0.98 ± 0.06	1.00 ± 0.05	–	–	MI > Sham***
MI (OLAD)	0.70 ± 0.08	1.30 ± 0.06	Reference	Reference	Reference
MICT	1.05 ± 0.07	1.12 ± 0.05	↓ vs MI**	↓ vs MI**	–
MIHIIT	1.12 ± 0.07	1.07 ± 0.05	↓ greater than MICT (p ≈ 0.046)	↓ vs MI**	–

Overall MANOVA: Wilks' $\Lambda = 0.312$, $F(8, 48) = 6.01$, $p < 0.001$, $\eta^2 = 0.50$

As shown in Table 3, induction of myocardial infarction (MI group) resulted in a significant increase in Cytochrome C and a significant decrease in *Survivin* compared with the healthy (Ct) and Sham groups ($p < 0.001$). Both training protocols (MICT and MIHIIT) significantly attenuated these changes and restored the values toward normal physiological levels. With regard to *Survivin*, interval training (MIHIIT) produced a greater increase than continuous training (MICT) ($p \approx 0.046$), whereas no significant difference between training types was observed for Cytochrome C (relative values). The changes in Cytochrome C across groups are schematically illustrated in Figure 1, where MI induction caused a significant elevation, while aerobic training protocols attenuated this increase.

Figure 1

Changes in Cytochrome C Across Study Groups



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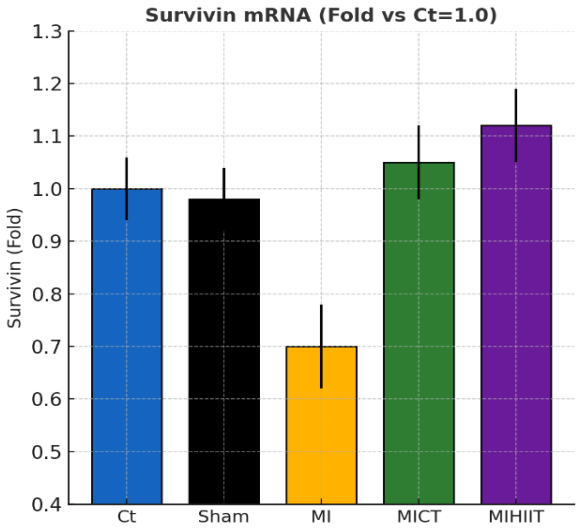
Similarly, changes in *Survivin* gene expression across the groups are schematically illustrated in Figure 2; myocardial infarction significantly reduced *Survivin*, while aerobic training increased its expression and restored it toward natural levels.

Figure 2

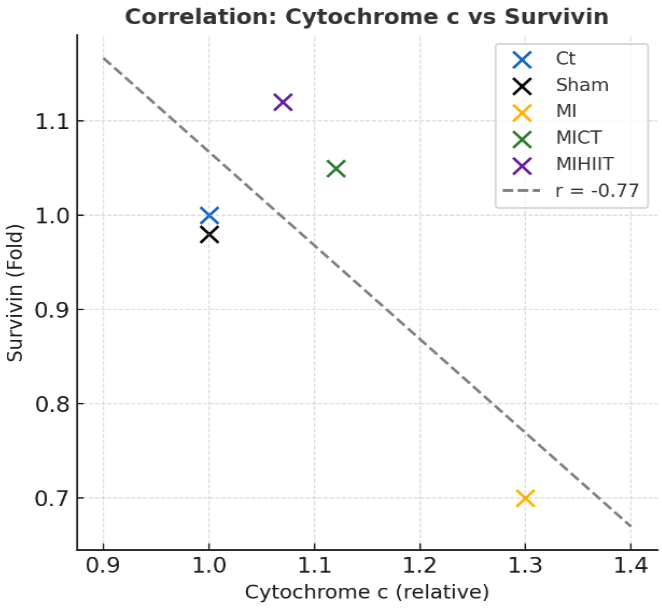
Survivin Gene Expression in Myocardial Tissue of Rats Modeled with Myocardial Infarction



To examine the relationship between oxidative stress and apoptotic pathways, the correlations between variables are shown in Figure 3. The results indicated a negative correlation between Cytochrome C and *Survivin*, such that increases in Cytochrome C were associated with decreases in *Survivin* expression. This pattern suggests that reductions in oxidative stress indices resulting from exercise training may be directly associated with reductions in apoptosis and enhanced survival of myocardial cells.

Figure 3

Relationship Between Oxidative Stress Index and Apoptotic Pathway in Myocardial Tissue



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4. Discussion and Conclusion

The present study examined the comparative effects of moderate-intensity continuous training (MICT) and high-intensity interval training (MIHIIT) on *Survivin* gene expression and Cytochrome C levels in myocardial tissue of rats with induced myocardial infarction. The findings demonstrated three core outcomes: (a) myocardial infarction significantly increased Cytochrome C and reduced *Survivin* expression, (b) both aerobic exercise protocols reversed these molecular disruptions, and (c) MIHIIT exerted a more pronounced effect on increasing *Survivin* expression, while reductions in Cytochrome C were similar across both training types.

The observed increase in Cytochrome C among MI rats reflects the establishment of mitochondrial apoptotic signaling, consistent with evidence showing that ischemia and reperfusion promote ROS-driven mitochondrial destabilization and cytochrome release (4). Cytochrome C is a proven marker of apoptosis, and its elevation has been reported across numerous MI models, including rodent studies demonstrating its role as a terminal mediator of cardiomyocyte death (3). Elevated oxidative stress in MI leads to mitochondrial permeability transition pore (mPTP) opening and the dissemination of apoptogenic proteins, a process well documented in MI-induced injury (21). In accordance with previous research, our data confirm that the LAD occlusion model triggers classical apoptotic pathways, producing substantial oxidative burden and pro-apoptotic signaling (5).

In addition, the significant reduction in *Survivin* expression after MI is consistent with prior reports indicating that ischemic injury suppresses endogenous anti-apoptotic regulators. *Survivin*, a member of the inhibitor of apoptosis (IAP) family, is essential in inhibiting caspase activation and promoting cardiomyocyte survival. Reduced *Survivin* expression under ischemic conditions has been previously demonstrated in experimental MI models and is understood to facilitate apoptotic progression (3). The current findings corroborate these mechanistic pathways, demonstrating that MI not only activates intrinsic apoptotic signaling but also disrupts protective gene networks critical for cardiomyocyte resilience.

A major contribution of this study is the demonstration that both MICT and MIHIIT significantly reversed MI-induced alterations in *Survivin* and Cytochrome C. Aerobic training is known to promote mitochondrial efficiency, reduce oxidative stress, enhance antioxidant enzyme activity, and downregulate apoptotic pathways (1). These mechanisms likely underlie the reduction in Cytochrome C observed in both training groups. Exercise also facilitates mitochondrial biogenesis and improves mitochondrial membrane integrity, decreasing the likelihood of Cytochrome C release into the cytosol (22). These results align with findings from rat models in which aerobic training reduced mitochondrial apoptotic markers, preserved mitochondrial ultrastructure, and improved left ventricular function following MI (5). Other exercise-based interventions have similarly demonstrated reductions in oxidative stress indices in cardiotoxicity and ischemia models (13).

The increase in *Survivin* expression following both training protocols is also consistent with prior data indicating that aerobic exercise enhances gene pathways associated with cellular survival and anti-apoptotic regulation. Interval and continuous training have been shown to increase expression of cardioprotective genes such as PP2Ac, GSK-3β, and others involved in cell survival signaling cascades (6). The modulation of inflammatory and metabolic pathways by aerobic training, such as the Ido1-KYN-Ahr axis, further supports the holistic cellular adaptations induced by exercise (17). By enhancing mitochondrial function and decreasing ROS accumulation, exercise establishes intracellular conditions favorable to *Survivin* transcription and translation, helping preserve cardiomyocyte viability.

One of the key findings of this study is that MIHIIT produced significantly greater increases in *Survivin* expression compared to MICT, despite both protocols similarly reducing Cytochrome C. This aligns with a substantial body of evidence showing that interval training may produce superior molecular adaptations compared with continuous training. Previous meta-analyses and controlled trials have demonstrated that HIIT is more effective in improving peak VO_2, endothelial function, electrophysiological remodeling, and cardiac autonomic responses in MI patients (7, 20). These enhanced

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physiological adaptations may translate into superior intracellular signaling changes, resulting in greater upregulation of anti-apoptotic genes such as *Survivin*. Experimental studies have similarly shown that HIIT modulates apoptosis more strongly than MICT, decreasing oxidative stress markers, reducing caspase activity, and enhancing anti-apoptotic responses in rodent heart failure models (10). Moreover, studies in clinical populations reveal that interval training activates more robust mitochondrial adaptations and oxidative capacity enhancements, which may explain the enhanced *Survivin* response (8).

The superior effect of MIHIIT on *Survivin* is further supported by prior evidence demonstrating that intermittent training induces more powerful metabolic and genetic responses in cardiac tissue compared to continuous training. For instance, HIIT has been shown to produce stronger effects on adipose tissue browning, metabolic gene expression, and mitochondrial biogenesis regulators (19). Although these studies focus on peripheral tissues, they collectively illustrate the more intense systemic stimulus produced by interval training. Given that *Survivin* expression is highly responsive to changes in intracellular redox status and energetic conditions, the heightened training intensity of MIHIIT may yield superior signaling cues conducive to its upregulation.

Nevertheless, both training modalities effectively reduced Cytochrome C levels to comparable degrees, suggesting that continuous and interval training share similar mechanisms in modulating mitochondrial permeability and oxidative stress. This is consistent with findings showing that both training modalities decrease ROS levels, enhance antioxidant enzymes, and reduce apoptotic markers in preclinical and clinical models (23). Comparative studies have similarly demonstrated that although HIIT may exceed MICT in improving certain parameters, both modalities usually exert similar influence on oxidative stress biomarkers (9).

The negative correlation observed between Cytochrome C and *Survivin* in this study reflects the reciprocal relationship between pro-apoptotic and anti-apoptotic pathways. This pattern supports the model of regulated cell death described in recent literature, which emphasizes the complexity and interactive nature of apoptotic signaling (3). As oxidative stress and mitochondrial instability increase, *Survivin* expression tends to decrease, exacerbating apoptotic progression. Conversely, interventions that support mitochondrial integrity simultaneously suppress apoptotic signals and promote *Survivin* upregulation. This bidirectional relationship underscores the biological plausibility of our findings and supports the concept of exercise as a potent modulator of cell survival pathways (1).

The findings of this study also reflect broader trends in the literature emphasizing the therapeutic potential of structured exercise as a cardioprotective intervention following MI. Exercise improves ventricular function, attenuates myocardial inflammation, regulates apoptotic pathways, and reverses pathological remodeling (22). Reviews of rehabilitation strategies similarly emphasize the necessity of integrating structured aerobic training—especially HIIT—into post-MI care due to its favorable risk-to-benefit ratio (2). Even digital platforms designed to promote physical activity after MI recognize the established benefits of exercise for long-term cardiac recovery (14).

Finally, the methodological frameworks applied in this study—including sample size calculations and standardized exercise protocols—align with best practices in preclinical research. Sample size estimation based on structured statistical guidelines (16) and training intensity prescriptions informed by VO_2max characteristics in rodent models (18) strengthen the validity of the obtained findings.

Collectively, the results of this study contribute to the growing literature demonstrating that both continuous and interval aerobic training exert beneficial effects on apoptotic and anti-apoptotic markers following myocardial infarction, with MIHIIT displaying superior capacity for enhancing *Survivin* expression. These findings reinforce the importance of structured exercise as a powerful therapeutic strategy for improving myocardial cellular resilience after ischemic injury.

This study was conducted on an animal model, which limits direct generalization to human clinical populations. The duration of the training protocol, though sufficient for molecular assessment, may not fully reflect long-term remodeling processes. Additionally, only two training intensities were examined, and other forms of exercise such as resistance training or combined modalities were not explored. Finally, the study measured only *Survivin* and Cytochrome C, while many other apoptotic and

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mitochondrial pathways could contribute to cardioprotection.

Future studies should investigate longer-term training interventions to determine whether the molecular benefits observed translate into structural and functional cardiac improvements. Expanding molecular analyses to include necroptosis, ferroptosis, and inflammatory markers would provide a more complete understanding of exercise-induced cardioprotection. Research comparing exercise with pharmacological interventions or combination therapies would also be valuable. Multi-modal exercise regimens should be studied to determine whether synergistic effects exist across training types.

Exercise professionals should consider incorporating both interval and continuous aerobic training into cardiac rehabilitation programs, knowing that each modality confers significant molecular benefits. Clinicians may emphasize interval training for patients who can safely tolerate higher intensities, as it may yield greater cellular resilience. Rehabilitation protocols should remain personalized, progressive, and closely monitored to ensure optimal safety and efficacy.

Authors' Contributions

All authors contributed substantially to the conception and design of the study, data collection, data analysis, and interpretation of results. Each author participated in drafting and critically revising the manuscript for important intellectual content, and all authors approved the final version for publication.

Declaration

In order to correct and improve the academic writing of our paper, we have used the language model ChatGPT.

Transparency Statement

Data are available for research purposes upon reasonable request to the corresponding author.

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Declaration of Interest

The authors report no conflict of interest.

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Ethics Considerations

This study was reviewed and approved by the Ethics Committee of the Islamic Azad University, Najafabad Branch, under the ethical approval code IR.IAU.NAJAFABAD.REC.1404.084. All procedures involving animals were conducted in accordance with the ethical guidelines and regulations of the committee, ensuring adherence to the principles of the national laboratory animal care guidelines. Handling of animals (choose appropriate) followed all institutional and international standards of ethical conduct.

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