Effects of resistance training following bone marrow stem cell transplantation on cardiac oxidative stress and left ventricular function in a rat model of myocardial infarction

Running title: Resistance training after stem cell transplantation in myocardial infarction model rats

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Abstract

Background: This study aimed to evaluate the effects of resistance training following bone marrow stem cell transplantation, **a regenerative approach targeting damaged cardiac tissue**, on myocardial oxidative stress markers and left ventricular function in a rat model of myocardial infarction (MI).

Methods: Sixty male Wistar rats (7–8 weeks old) were randomly assigned to six experimental groups (n=10 per group): healthy control, MI control, sham, stem cell, exercise, and exercise + stem cell. MI was induced by permanent ligation of the left anterior descending coronary artery. Stem cells (1×10^6) were injected via the tail vein. Resistance training protocol consisted of climbing sessions performed five days per week for six weeks. Each session included three sets of five repetitions, with a one-minute rest interval between sets. Oxidative stress markers (CAT and MDA) were analyzed biochemically, and left ventricular function was assessed by echocardiography. Data were analyzed using one-way ANOVA and Tukey's post hoc test.

Results: MDA levels were significantly increased and CAT levels decreased in the MI group compared to controls. Resistance training and combined therapy significantly reduced MDA levels; however, CAT changes were not statistically significant. Cardiac output and ejection fraction were significantly improved in the intervention groups compared to the MI group.

Conclusion: Six weeks of resistance training after bone marrow stem cell transplantation effectively reduced oxidative stress and improved left ventricular function in MI rats. This combined approach may serve as a promising therapeutic strategy for myocardial infarction recovery.

Keywords: Resistance training, Stem cell, Oxidative stress, Left ventricular function, Myocardial infarction

Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality in many societies, accounting for approximately 32% of all deaths worldwide(1). One of the most common CVDs is myocardial infarction (MI) which occurs when blood flow through one of the coronary arteries is reduced or completely blocked, resulting in infarction (tissue death) of the heart muscle. Scientific evidence indicates that, within 90 days post-MI, significant hemodynamic and ventricular abnormalities may develop, including impaired systolic and diastolic function, reduced cardiac output, decreased systolic blood pressure, and downregulation of the SERCA2 gene in the myocardial sarcoplasmic reticulum (2). Despite advances in diagnosis and treatment, current therapies for MI remain largely palliative, emphasizing the urgent need for innovative regenerative strategies to restore cardiac structure and function.

Experimental studies suggest that myocardial regeneration via stem cell transplantation may offer a promising alternative for MI treatment(3). Stem cell therapy has recently emerged as an innovative approach, aiming to restore lost cardiomyocytes and promote repair of the damaged myocardium(4,5). Among the various stem cells investigated, mesenchymal stem cells (MSCs) have become one of the most widely studied cell types in regenerative medicine. Although initially believed to have cardiomyogenic differentiation potential, MSCs' relatively low immunogenicity compared to other bone marrow-derived stem cell types is considered one of their key advantages (6). Allogeneic MSCs, sourced from young and healthy donors, also offer enhanced proliferative capacity. Furthermore, these cells have demonstrated the ability to differentiate into vascular lineages and express key proteins required for electrical integration with neighboring cardiomyocytes (7). Previous animal studies have demonstrated that transplantation of bone marrow-derived MSCs or mononuclear cells improves myocardial perfusion, reduces infarct size, and enhances contractility in both acute and chronic ischemic models (8,9), highlighting their therapeutic potential for cardiac repair.

In addition, exercise training has been identified as an effective strategy for minimizing cardiac injury and reducing cardiovascular morbidity and mortality (8). One of the key long-term benefits of exercise is its anti-inflammatory effects and enhancement of antioxidant defense mechanisms, both of which play a critical role in neutralizing free radicals (9). While most research has focused on the use of aerobic training for cardiac rehabilitation(10), studies on the therapeutic effects of resistance training following MI remain limited, despite its potential benefits(11). Although both resistance exercise and bone marrow stem cell transplantation have shown promising effects in the treatment of myocardial infarction, few studies have investigated their combined impact on oxidative stress markers and cardiac function. Therefore, the present study aims to evaluate the effects of resistance training following bone marrow stem cell transplantation on myocardial oxidative stress and left ventricular function in a rat model of myocardial infarction.

Methods

In this study, 60 male Wistar rats, aged 7 to 8 weeks, were used. The animals were housed in a standard laboratory environment designed for rodents, with free access to water and a standard rodent diet. The animals were maintained under controlled conditions at a temperature of 22–24°C, relative humidity of 55%–60%, and a 12:12-hour light-dark cycle. All experimental procedures were conducted in accordance with the ethical principles of animal care, and the study was approved by the Ethics Committee of Islamic Azad University, Sari Branch, with the approval code IR.IAU.SARI.REC.1404.110. The animals were randomly divided into six groups of ten rats each: healthy control, sham, myocardial Infarction (MI), myocardial infarction with cell

transplantation (MI-Cell), myocardial infarction with resistance training (MI-Re), and myocardial infarction rats with cell transplantation + resistance training (MI-Cell+Re).

To induce MI, the animals were anesthetized using intraperitoneal injection of thiopental sodium (50 mg/kg, IP). The thoracic region was shaved thoroughly, and the rats were placed in a supine position on a sterile surgical platform. Heparin (200 U/kg) was administered to prevent intraoperative coagulation. To facilitate tracheal access, the animal's neck was gently extended and positioned appropriately for endotracheal intubation. After intubation, the rats were connected to a small animal ventilator (Harvard Apparatus Model 683, USA) to ensure controlled respiration throughout the procedure. A left thoracotomy was performed via the fourth intercostal space, exposing the heart. Particular care was taken to avoid damaging the left lung or cardiac tissue during the incision. The pericardium was then carefully opened to access the coronary arteries. A 6-0 silk suture was passed beneath the left anterior descending (LAD) coronary artery, and permanent occlusion was achieved by ligation of the vessel. Successful induction of infarction was confirmed by monitoring lead II ECG using the PowerLab data acquisition system (Harvard, USA), typically evidenced by ST-segment elevation. During surgery, the animals' core body temperature was maintained at $37 \pm 1°C$ using a regulated heating pad. After the procedure and upon full recovery from anesthesia, the animals were returned to individual cages with free access to food and water and were transferred to the animal facility for further care (9).

Bone marrow–derived mesenchymal stem cells (BM-MSCs) transplantation

For the isolation of bone marrow–derived mesenchymal stem cells (BM-MSCs), five male Wistar rats (6 weeks old) were used. After complete anesthesia, the femurs and tibias of the animals were surgically removed under sterile conditions. The bone marrow was flushed out and subjected to centrifugation at 1200 rpm for 10 minutes. The isolated cells were then cultured in Minimum Essential Medium Alpha (MEM-α; PAA, Pasching, Austria) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. After three consecutive passages, the adherent mesenchymal stem cells were trypsinized, re-centrifuged at 1200 rpm for 10 minutes, and prepared for transplantation. To confirm the mesenchymal phenotype of the cells, immunocytochemistry was performed using antibodies against CD71 and CD90 surface markers. Following confirmation, the cells were washed with phosphate-buffered saline (PBS) and resuspended by pipetting in culture medium. Cell counting was performed using a Neubauer hemocytometer, and a suspension containing approximately 1×10^6 cells/μL in PBS was prepared for injection. Immediately after MI induction, BM-MSCs were administered via tail vein injection (1 μL per rat) (12).

Resistance training

One week before myocardial infarction induction, animals were acclimated to the apparatus over three consecutive days before starting the formal training. Resistance training protocol consisted of climbing five days per week for six weeks. Each session consisted of three sets with five repetitions, with a one-minute rest interval between sets. The exercise was performed after attaching weights to the tails of the rats at one day after MI induction. In the first week, the weight attached to each rat's tail was equivalent to 50% of its one-repetition maximum (1RM), which was determined the day before the onset of the resistance training. This load was increased by 10% each week, reaching 100% of 1RM in the final week. Two weeks before the formal training, animals were familiarized with ladder climbing; rats that initially refused were gently encouraged to climb using manual stimulation. All sessions were supervised to ensure animal safety and compliance. Control animals were handled similarly but did not undergo any exercise protocol.

Echocardiographic Assessment

Echocardiographic measurements were performed using a high-frequency ultrasound imaging system suitable for small animals, such as the Vevo 2100 (VisualSonics Inc., Toronto, Canada), equipped with a 12 MHz linear-array transducer, 2 days after last exercise session. Prior to imaging, rats were anesthetized with an intraperitoneal injection of ketamine (60 mg/kg) and xylazine (15 mg/kg) to minimize movement while preserving cardiac function. Body temperature was maintained at 37°C using a heated platform throughout the procedure. The chest area was shaved, and acoustic coupling gel was applied to enhance signal quality. M-mode echocardiographic images were acquired in the parasternal long-axis and short-axis views to evaluate left ventricular (LV) structure and function. Key parameters, including left ventricular ejection fraction (EF), and cardiac outpot (CO), were measured from M-mode tracings at the mid-papillary level. Measurements were averaged over three consecutive cardiac cycles for accuracy (9,13).

Collection of heart tissues

One day after echocardiography assessment, the rats were anesthetized via intraperitoneal injection of a higher dose of thiopental sodium. The hearts were excised, rinsed with PBS, and the non-infarcted regions of the left ventricle were dissected within 2 minutes on ice. The tissues were then placed in 2 mL microcentrifuge tubes and stored at −80 °C for subsequent analyses. Tissue homogenization was performed using 1 mL of ice-cold lysis buffer containing 1.5 mM $MgCl_2$, 0.1% Triton X-100, 10 mM NaCl, 20 mM HEPES, 20% glycerol, and 1 mM dithiothreitol (pH 7.4). The homogenates were centrifuged at 10,000 × g for 15 minutes at room temperature, and the resulting supernatants were stored at −80 °C for later assessments.

Oxidative stress evaluation

Catalase (CAT) Activity Measurement

Catalase activity was determined using the method described by Aebi (14). Briefly, 1 mL of 50 mM potassium phosphate buffer (pH 7.0) was added to the homogenized tissue sample, followed by the addition of 50 µL of H_2O_2. The absorbance was measured at 240 nm using a spectrophotometer against a blank, and changes in absorbance were recorded over a 3-minute period in 30-second intervals.

Malondialdehyde (MDA) Measurement

To assess MDA levels, the method established by Hermann Esterbauer et al. (15) was followed. The left ventricular tissue was homogenized in 50 mM Tris–HCl buffer (pH 7.4) and centrifuged at 12,000 × g for 10 minutes. Then, 50 µL of the supernatant was combined with 500 µL of 0.67% thiobarbituric acid (TBA) and 500 µL of 20% trichloroacetic acid (TCA). The mixture was incubated in a boiling water bath at 100 °C for 20 minutes. After cooling to room temperature, the samples were centrifuged at 4,000 × g for 10 minutes, and the absorbance of the supernatant was read at 532 nm using a spectrophotometer.

Statistical analyses

Descriptive and inferential statistics were used for data analysis. The Shapiro–Wilk test was employed to assess the normality of data distribution. One-way analysis of variance (ANOVA) was used to examine differences in the study variables among groups. In cases where significant differences were observed, the Tukey post hoc test was conducted to identify the specific group differences, with a significance level set at $P \leq 0.05$. All statistical analyses were performed using SPSS software, version 20.

Results

Oxidative stress indices

Catalase (CAT) Activity in Cardiac Tissue

The results of the one-way ANOVA for catalase (CAT) levels in cardiac tissue revealed a statistically significant difference among the experimental groups ($F = 3.637$, $P = 0.007$), indicating that CAT levels varied significantly between groups. Consequently, suggesting that resistance training following bone marrow stem cell transplantation exerts a significant effect on cardiac CAT levels in rats with myocardial infarction (MI). Tukey's post hoc test, as presented in Figure 1, identified significant differences specifically between the infarcted (MI) group and both the control and sham groups. Although CAT levels were elevated in the exercise, stem cell, and combined exercise + stem cell groups compared to the infarcted group, these increases did not reach statistical significance (Chart 1).

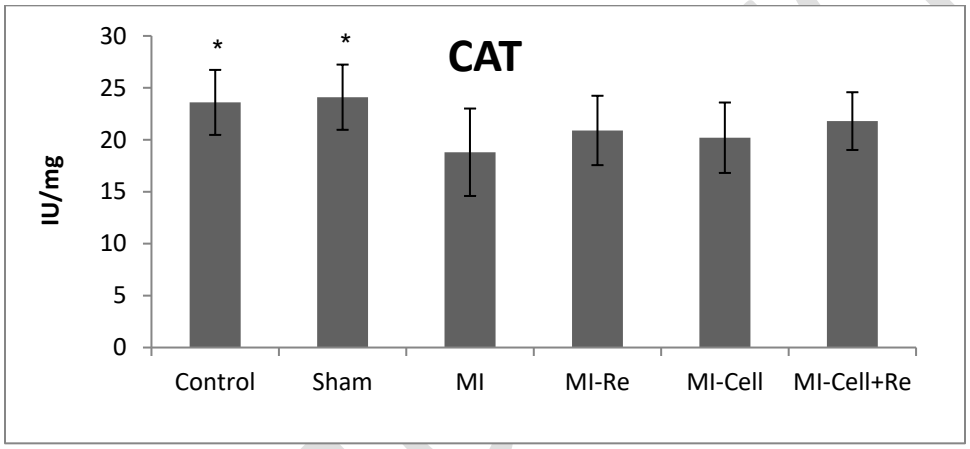

Figure 1. CAT levels in research groups
***.** Sign of significant difference with the MI group

Malondialdehyde (MDA) Levels

One-way ANOVA for malondialdehyde (MDA) levels across groups showed a highly significant effect ($F = 587.269$, $P < 0.001$), confirming substantial intergroup differences. As a result, indicating that resistance training in combination with bone marrow stem cell transplantation significantly alters MDA levels in the cardiac tissue of rats with MI. Tukey's post hoc analysis (Figure 2) revealed that MDA levels were significantly higher in the infarcted group than in the control and sham groups. Additionally, both the resistance training group and the combined training + stem cell group demonstrated a significant reduction in MDA levels compared to the infarcted group. Although the cell-only group showed a reduction in MDA levels relative to the infarcted group, this difference was not statistically significant.

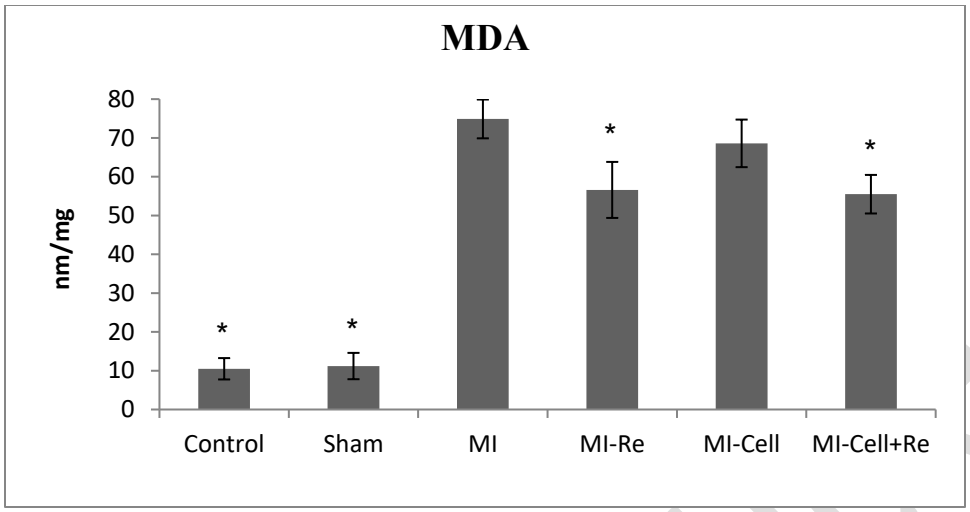

Figure 2. MDA levels in research groups
***.** Sign of significant difference with the MI group

Cardiac Function
Ejection Fraction (EF)
One-way ANOVA revealed a significant difference in ejection fraction values among the groups ($F = 132.687$, $P < 0.001$). These findings suggest that resistance training following bone marrow stem cell transplantation has a significant effect on ejection fraction in rats with MI. According to Tukey's post hoc analysis and the group comparisons illustrated in Figure 3, the infarcted group exhibited a markedly reduced ejection fraction compared to the control and sham groups. In contrast, the resistance training, cell, and combined training + cell groups all showed significant improvements in ejection fraction compared to the infarcted group.

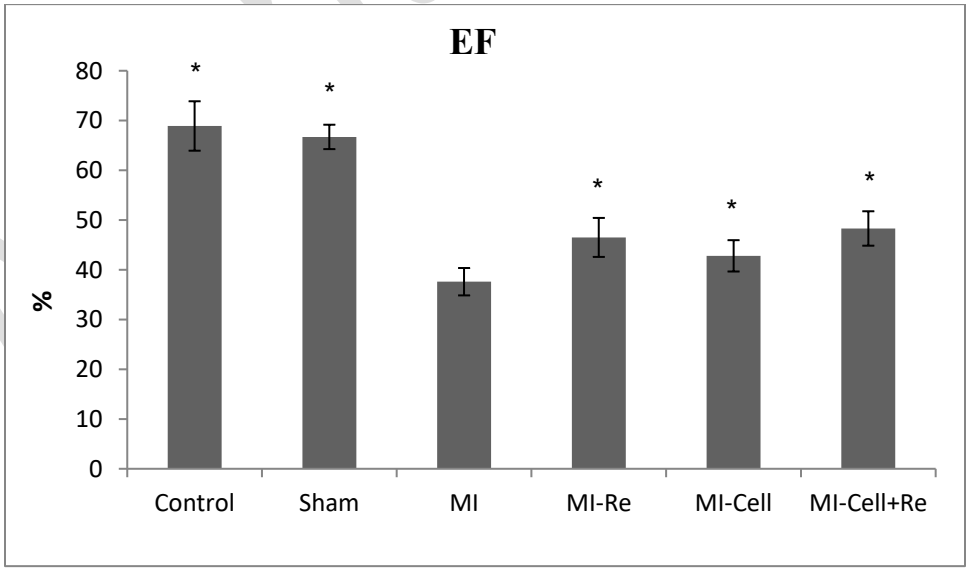

Figure 3. MDA levels in research groups
***.** Sign of significant difference with the MI group

Cardiac Output (CO)

Similarly, one-way ANOVA for cardiac output revealed statistically significant differences among groups ($F = 154.434$, $P < 0.001$). These findings confirm that resistance training in combination with bone marrow stem cell transplantation significantly influences cardiac output in MI model rats. Post hoc comparisons (Figure 4) demonstrated that cardiac output was significantly reduced in the infarcted group relative to the control and sham groups. Conversely, the resistance training, cell transplantation, and combined resistance training + cell therapy groups showed significant increases in cardiac output compared to the infarcted group.

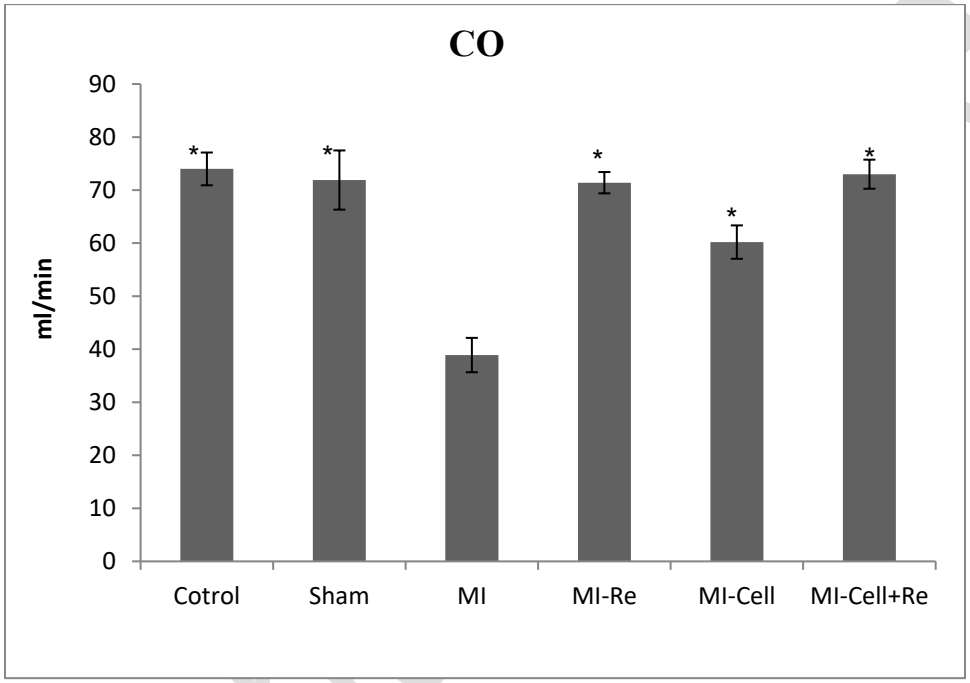

Figure 4. MDA levels in research groups
***.** Sign of significant difference with the MI group

Discussion

The present study investigated the effects of resistance training following bone marrow stem cell transplantation on oxidative stress markers and cardiac function in a rat's model of myocardial infarction. The findings demonstrated that this combined intervention significantly reduced oxidative stress-evidenced by increased Catalase activity and decreased malondialdehyde levels-and improved cardiac performance, particularly in terms of ejection fraction and cardiac output. These results support the growing body of evidence that highlights the synergistic potential of combining exercise training with regenerative cell-based therapies to promote cardiac recovery following ischemic injury.

Our findings are partially consistent with those reported by Ranjbar et al. (2016), who observed that 10 weeks of moderate-intensity exercise in rat with MI significantly reduced MDA and increased serum glutathione peroxidase levels. However, their study also reported no significant changes in catalase or myeloperoxidase activity (9). Similarly, in our study, although CAT levels showed an increasing trend in the resistance training, stem cell therapy, and combined treatment groups, these increases did not reach statistical significance. These discrepancies could be

attributed to differences in the duration, intensity, and type of exercise protocol used, as well as tissue-specific responses to oxidative stress.

It is well established that physical exercise elevates oxygen consumption up to 10–20 fold, thereby inducing a range of physiological responses including the upregulation of cytokines, tumor necrosis factor-alpha (TNF-α), corticosteroids, and adenosine (16). These factors can modulate the activity of endogenous antioxidant enzymes. Moreover, exercise enhances the expression of these enzymes through activation of nuclear transcription factors such as NF-κB. Nonetheless, the magnitude and pattern of antioxidant enzyme responses are highly dependent on the duration and intensity of exercise, which may explain the selective increases in certain enzymes observed in both the current and previous studies (17).

From a functional perspective, our results showed that cardiac ejection fraction and cardiac output were significantly impaired in the infarcted group, as expected. However, these indices were markedly improved in all intervention groups, particularly in those receiving both resistance training and stem cells therapy. This suggests that the combined intervention may enhance myocardial recovery by reducing end-systolic volume and facilitating more effective contractile function of the left ventricle.

Mechanistically, it is plausible that regular resistance training enhances the homing and integration of transplanted stem cells into the ischemic myocardium (18,19). Exercise may stimulate the release of angiogenic and anti-apoptotic mediators such as vascular endothelial growth factor (VEGF), placental growth factor (PGF), granulocyte colony-stimulating factor (G-CSF), stromal cell-derived factor-1 (SDF-1), and other cytokines that promote stem cell migration, survival, and differentiation. Furthermore, exercise may enhance telomerase activity, contributing to cellular longevity and regenerative potential (20,21,22). Several physiological mechanisms may underlie the observed improvements in cardiac function following exercise training in myocardial infarction models. Resistance exercise enhances myocardial contractility by improving calcium handling and excitation–contraction coupling in cardiomyocytes. It also reduces afterload through decreased peripheral vascular resistance, facilitating more efficient cardiac output. Adaptive left ventricular hypertrophy induced by training increases stroke volume without pathological remodeling. Moreover, resistance training upregulates endogenous antioxidant defenses—including catalase, superoxide dismutase, and glutathione peroxidase—leading to reduced oxidative damage (23). It also promotes angiogenesis by increasing expression of VEGF and PGF, thus improving perfusion in ischemic regions (24). Improvements in endothelial function via enhanced nitric oxide availability, as well as the suppression of apoptosis through modulation of Bcl-2 and Bax proteins (25), further support myocardial recovery. Additionally, activation of survival pathways such as PI3K/Akt, improved calcium homeostasis (26), and reductions in systemic inflammation (27) contribute to the cardioprotective effects of resistance training. Collectively, these mechanisms highlight the multifactorial benefits of resistance exercise as an adjunctive strategy in cardiac rehabilitation.

Taken together, the results of the present study suggest that the combination of resistance exercise and bone marrow stem cell transplantation can effectively attenuate oxidative damage and improve cardiac function in the setting of myocardial infarction. Taken together, our findings highlight a clear relationship between oxidative stress markers (MDA and CAT) and cardiac function, demonstrating that interventions which reduce oxidative damage are closely associated with improvements in ejection fraction and cardiac output. These findings underscore the importance of incorporating structured physical activity into regenerative medicine protocols aimed at cardiovascular repair.

Conclusion

Overall, the results of the present study showed that six weeks of regular resistance training after bone marrow stem cell transplantation reduced oxidative stress (indicated by decreased MDA and increased CAT) and improved left ventricular function in rats with myocardial infarction. These findings demonstrate a clear relationship between oxidative stress markers and cardiac function, suggesting that interventions which reduce oxidative damage are associated with improved ejection fraction and cardiac output. Therefore, this combined therapeutic approach may improve the condition of patients with myocardial infarction and can be considered a promising therapeutic strategy.

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Ethical Statement

All experiments were performed in the Animal Ethics Committee of Islamic Azad University, Sari Branch (Ethical code: IR.IAU.SARI.REC.1404.110).

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Author Contributions

All authors contributed to designing the study, analyzing and interpreting data, writing the manuscript, and approving the final submission.

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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