

Review

Exercise Training and Cardioprotection in Cardiovascular Disease: A Review of Mechanisms

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Abstract

Cardiovascular disease remains the leading cause of death worldwide, prompting extensive research into effective methods for treatment and prevention. Among these, exercise training and physical activity are widely recognized as the safest and most effective strategies for improving health. Specifically, exercise training has been explored for its role in cardioprotection, particularly in reducing damage caused by ischemia-reperfusion (I/R) injury and myocardial infarction (MI). Both high-intensity interval training (HIIT) and moderate-intensity continuous exercise (MICE) have been investigated for their potential to induce cardioprotection. Aerobic exercise, in particular, is known to minimize I/R injury through multiple mechanisms, including exercise preconditioning. This review aims to examine the underlying mechanisms by which exercise training confers cardioprotective effects after MI. A systematic review of the literature was conducted using Google Scholar and PubMed with the keywords: exercise training, cardioprotection, preconditioning, cardiovascular disease, and myocardial infarction. Over 50 articles were initially identified, and 37 were selected for detailed analysis. The findings reveal several mechanisms by which exercise training promotes cardioprotection, including the reduction of cardiovascular risk factors, attenuation of oxidative stress, modulation of inflammation, enhancement of myocardial cell proliferation,



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and regulation of microRNAs. Among these, the most widely recognized mechanism is exercise-induced preconditioning, which improves the heart's resilience to I/R injury through activation of protective pathways. In conclusion, this review highlights that exercise training, particularly aerobic exercise, can significantly enhance cardiac resistance to ischemia-reperfusion (I/R) injury. Through preconditioning, exercise fortifies the heart, reduces ischemic damage, and contributes to better cardiovascular outcomes. Future research should continue to investigate these mechanisms to optimize exercise-based interventions for individuals at risk of cardiovascular events.

Keywords

Cardiovascular disease; exercise preconditioning; cardioprotective; exercise training; myocardial infarction

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, accounting for significant healthcare expenditures related to treatment, research, and prevention efforts [1]. The cardiovascular system is intricately connected to the overall health and function of the body's systems. One of the most effective methods for preventing and treating cardiovascular disease is regular exercise, which promotes heart health by improving blood flow, enhancing nutrient delivery, and protecting against further deterioration of heart function [2].

Atherosclerosis, the most dangerous and life-threatening mechanism of coronary artery disease, results from blockages in the coronary arteries caused by factors such as fatty plaques, chronic stress, anxiety, physical inactivity, and other risk factors. Management often involves pharmacological treatments, coronary artery bypass grafting (CABG), and other interventions, followed by cardiac rehabilitation programs. These programs aim to help patients reintegrate into society, the workplace, and family life while improving their cardiovascular health [3].

Research continues to explore the optimal exercise programs for cardiac rehabilitation and prevention. Among these, the concept of cardioprotection has gained significant attention. Cardioprotection refers to strategies that prevent or mitigate heart damage, particularly following ischemic events. Exercise training has emerged as a cornerstone of cardioprotection, with high-intensity interval training (HIIT) and moderate-intensity continuous exercise (MICE) being two key modalities [4, 5]. Studies suggest that HIIT is not only more tolerable for many patients but also safer and more effective for rehabilitation after CABG and other cardiac conditions compared to MICE [4].

By carefully tailoring exercise programs in terms of intensity, frequency, and duration, and incorporating a heart-healthy diet, patients can maintain vascular elasticity, strengthen the heart, and reduce the risk of future cardiac events. Exercise-induced cardioprotection encompasses four broad areas: 1) cardiovascular disease (CVD) risk factor improvement, 2) anatomical remodeling of the heart, 3) improved cardiac physiologic function, and 4) mechanisms of exercise preconditioning [6].

In summary, the cumulative evidence highlights the importance of exercise training as a pivotal strategy for preventing, treating, and rehabilitating cardiovascular disease. By focusing on structured

exercise protocols, such as HIIT and MICE, along with lifestyle modifications, cardioprotective benefits can be maximized, thereby paving the way for improved patient outcomes.

2. Materials and Methods

This review article examined current research findings related to the mechanisms of exercise-induced cardioprotection. A comprehensive literature search was conducted using the keywords: *exercise training*, *cardioprotection*, *preconditioning*, *cardiovascular disease*, and *myocardial infarction* on two major scientific databases—Google Scholar and PubMed.

The initial search yielded more than 53 relevant articles. After a thorough review, 43 articles were shortlisted based on the following inclusion criteria:

- Clear relevance to exercise and cardioprotection.
- Presence of the keywords (cardioprotection, exercise, and mechanisms) in the title or abstract.
- High publication quality, judged by the reputation of the journal.

Following further assessment, 40 articles were ultimately selected for inclusion in this review. These sources were analyzed to provide a comprehensive understanding of how exercise training contributes to cardioprotection through physiological, biochemical, and molecular pathways.

3. Results

3.1 Inactivity: The Main Cause of Chronic Diseases

Exercise training is widely recognized as one of the most effective methods for treating and preventing chronic diseases [7, 8]. Sedentary individuals face a 20–30% higher risk of mortality compared to physically active individuals, who tend to exhibit improved cardiovascular health, greater physical fitness, and a lower likelihood of developing chronic diseases such as cardiovascular disorders [8]. The detrimental consequences of physical inactivity include energy imbalance, oxidative stress, impaired glycemic control, inflammation, and vascular dysfunction. Collectively, these issues contribute to the development of obesity, cardiovascular disease, stroke, osteoporosis, cancer, and type 2 diabetes [7, 8].

Inactivity exacerbates many of the known risk factors for cardiovascular disease. Without consistent physical activity, even the most advanced therapeutic or preventive interventions may have limited impact. Prolonged sedentary behavior leads to excessive fat accumulation and elevated lipid levels in the bloodstream [9, 10].

This decline in activity often follows life transitions. While children and adolescents are typically active through school sports and recreational activities such as running or cycling, adulthood introduces increasing demands from work, family, and social obligations, resulting in a decrease in physical activity. Over time, this decline contributes to weight gain and increases the risk of cardiovascular disease. Additionally, poor dietary habits—such as frequent consumption of fast food and unsaturated fats—worsen metabolic imbalances, increasing low-density lipoprotein (LDL) and triglycerides while reducing beneficial high-density lipoprotein (HDL). This lipid imbalance accelerates the progression of atherosclerosis and coronary artery disease.

Furthermore, aging and inactivity contribute to sarcopenia, a degenerative condition marked by the loss of muscle mass and strength. Reduced muscle and nerve function impairs mobility and physical capacity, reinforcing a harmful cycle of inactivity and declining health [11]. Breaking this

cycle requires personalized, structured exercise programs, which are essential for restoring metabolic health and alleviating the burden of chronic diseases.

3.2 Cardioprotective Mechanisms of Exercise

Cardioprotection following exercise refers to a physiological state in which the heart becomes more resilient to ischemia-reperfusion (I/R) injury. This protective effect is attributed to various mechanisms, including the development of collateral coronary arteries, the induction of myocardial heat shock proteins, and enhanced cardiac antioxidant capacity [12]. Exercise is likely to promote cardioprotection by attenuating several cardiovascular risk factors [13].

During ischemia, oxygen delivery to myocardial tissue is impaired, disrupting mitochondrial energy production. This triggers a cascade of detrimental effects, including elevated reactive oxygen species (ROS), calcium (Ca^{2+}) overload, calpain activation, hydrogen ion (H^+) accumulation, and ATP depletion. Collectively, these changes contribute to mitochondrial dysfunction and the death of myocardial cells. Exercise-induced cardioprotection mitigates these effects through several key pathways:

- Increased nitric oxide (NO) production, enhancing vasodilation and myocardial blood flow.
- Improved antioxidant defenses that neutralize free radicals and reduce oxidative stress.
- Upregulation of heat shock proteins that protect cardiac cells from stress-induced injury.
- Activation of ATP-sensitive potassium channels, improving cellular energy regulation and resilience.
- Elevated cyclooxygenase-2 (COX-2) expression, which offers anti-inflammatory effects and boosts mitochondrial function [14, 15].

Exercise also exerts systemic effects by improving blood flow, neural signaling, and skeletal muscle function. These widespread adaptations extend to cardiovascular health, where exercise enhances the heart's ability to resist I/R injury [2, 16]. The multifaceted mechanisms of exercise-induced cardioprotection highlight its essential role in both cardiovascular disease prevention and rehabilitation.

3.2.1 Mental and Psychological Effects of Exercise

Daily life stressors—including job pressure, family duties, and social obligations—can lead to stress, depression, and other mental health issues. Physical activity, especially in group settings, significantly reduces these psychological burdens. For cardiac patients, especially those recovering from coronary artery disease or surgeries, exercise is a critical component of rehabilitation that enhances emotional well-being and reduces psychological distress [17].

3.2.2 Vagal Tone, Heart Rate Variability, and Exercise

Exercise enhances vagal tone by increasing heart rate variability (HRV), reflecting a more adaptive autonomic nervous system. Rhythmic physical activities, such as walking or running, stimulate parasympathetic activity, which lowers the resting heart rate and increases the heart rate reserve. These adaptations improve cardiovascular efficiency during exertion [18].

3.2.3 Thrombosis, Fibrinolysis, and Exercise

Exercise reduces the risk of thrombosis by decreasing platelet adhesion and enhancing fibrinolysis. The metabolic demands of physical activity enhance lipid metabolism, resulting in reductions in LDL and triglycerides, as well as increases in HDL. Additionally, regular exercise reduces blood pressure, inflammation, and adipocyte accumulation, while enhancing vascular compliance and endothelial function—all of which contribute to reduced cardiovascular risk [19-21].

3.2.4 Exercise and Nitric Oxide (NO)

Nitric oxide is a signaling molecule that modulates vascular tone, blood pressure, and tissue perfusion. Physical activity increases blood flow, triggering vascular remodeling through angiogenesis and slight dilation of the vessels. These effects are mediated by upregulation of eNOS, which enhances NO synthesis. The resulting NO boosts blood flow, reduces inflammation and oxidative stress, and improves microvascular function. Notably, high-intensity interval training (HIIT) raises NO metabolites (NO_2^- and NO_3^-), which serve as reservoirs that convert to NO during ischemic episodes, thereby minimizing reperfusion injury [22-25]. Ramez et al. (2019) demonstrated that HIIT provides greater cardioprotection from I/R injury than moderate-intensity continuous training (MICT) [5].

Regular exercise induces lasting adaptations that improve hemodynamics and reduce ischemia-reperfusion (I/R) injury through cellular and molecular pathways [26].

D'Haese et al. further demonstrated that both moderate-intensity and HIIT protocols confer equivalent cardioprotective benefits during the progression of type 2 diabetes in rats, albeit via different mechanisms. HIIT enhanced antioxidant systems (SOD2, glyoxalase), whereas MICT promoted anti-inflammatory macrophage markers (CD206, CD163). Future studies should explore how exercise intensity affects cardioprotection [27].

3.2.5 Heart Health and Cardioprotection with Exercise

Emerging research (2022) underscores exercise as a powerful non-pharmacologic intervention for cardiac health and protection. Exercise-induced cardioprotection is mediated through:

- Risk factor modification (improved lipid profile, BMI, and blood pressure).
- Reduced myocardial oxidative stress via lowered ROS and heightened antioxidant defense.
- Physiologic cardiac hypertrophy supported by cardiomyocyte proliferation and anti-apoptotic effects.
- Improved vascular response through endothelial function and angiogenesis.
- Enhanced metabolism via increased fatty acid oxidation, ATP generation, and glucose utilization.
- Systemic benefits affecting skeletal muscles, vasculature, brown adipose tissue, and gut microbiota [28].

These mechanisms collectively underscore the crucial role of exercise in enhancing cardiovascular health and slowing disease progression.

3.3 Other Pathways of Cardioprotection with Exercise

3.3.1 Mechanosensitive Ion Channels

Mechanosensitive ion channels, such as Piezo1 and TRP channels, are widely distributed in various organs, including the heart, lungs, and bladder. These channels play an essential role in maintaining cardiovascular function, particularly during physical activity. Through exercise, the activity of Piezo1 and TRP channels is modulated, contributing to improved blood pressure regulation and protection against cardiovascular conditions such as atherosclerosis, myocardial infarction, and cardiac fibrosis. By enhancing the function of these ion channels, exercise helps to prevent heart failure and promote cardiac resilience [29].

3.3.2 miR-210 and Exercise Training

Exercise-induced cardioprotection involves modulation of specific microRNAs, including miR-210. In a 2024 study by Bei et al., eight weeks of swimming in both wild-type (WT) and miR-210 knockout (KO) rats resulted in enhanced cardiomyocyte proliferation during physiological cardiac growth. This adaptation resulted in a significant reduction in ischemia-reperfusion (I/R) injury and increased myocardial protection, highlighting miR-210 as a key regulator of exercise-mediated cardioprotection [30].

3.3.3 AMPK and Exercise Training

AMPK (AMP-activated protein kinase) is a crucial signaling molecule that plays a vital role in maintaining energy homeostasis and protecting the heart. Exercise has been shown to increase AMPK phosphorylation, leading to beneficial adaptations in the cardiovascular system. Maufrais et al. (2024) reported that intradialytic exercise improved left ventricular mechanics and overall cardiac hemodynamics in patients, underscoring the central role of AMPK in mediating exercise-induced cardioprotective effects [31, 32].

3.3.4 Brown Adipose Tissue and Exercise Training

Zhao et al. (2022) identified brown adipose tissue as a novel contributor to exercise-induced cardioprotection [33]. Their findings demonstrated that brown fat releases small extracellular vesicles containing cardioprotective microRNAs. These vesicles are transported to the heart, where they enhance cellular resilience and reduce injury during physical stress, further emphasizing the systemic benefits of exercise on cardiovascular health [33].

3.3.5 HIPK2 and Exercise Training

Homeodomain-Interacting Protein Kinase 2 (HIPK2) is a multifunctional protein involved in cellular proliferation, apoptosis regulation, and mitochondrial dynamics. Emerging evidence suggests that HIPK2 plays a key role in exercise-induced cardiac remodeling. By modulating this kinase, exercise contributes to physiological cardiac hypertrophy, improved mitochondrial function, and overall cardioprotection [34].

3.3.6 Exercise Training and New Mechanisms of Cardioprotection

Guo et al. (2020) identified several novel molecules that contribute to exercise-induced cardioprotection in myocardial infarction (MI) [35]. Among these:

- Growth Differentiation Factor 15 (GDF15): Reduces inflammation in cardiomyocytes.
- Follistatin-like 1 (FSTL1): Prevents cardiac fibrosis and promotes angiogenesis.
- Irisin: Mitigates apoptosis and supports myocardial regeneration.
- Fibroblast Growth Factor 21 (FGF21): Prevents cell death, enhances capillary density, and activates the FGFR1/PI3K/AKT/VEGF signaling pathway to facilitate angiogenesis. Notably, FGF21 deficiency impairs exercise-induced angiogenesis in MI mouse models.

Additional cardioprotective factors include:

- Interleukin-33 (IL-33): Reduces apoptosis, inflammation, and fibrosis.
- Neuregulin (NRG): Decreases cardiomyocyte apoptosis.
- Migration Inhibitory Factor (MIF): Promotes angiogenesis and limits inflammation.

Exercise also triggers the release of microRNAs, such as miR-1, miR-133, miR-499, miR-126, and miR-21, which collectively act to prevent apoptosis, reduce inflammation, enhance angiogenesis, and promote cardiac growth and regeneration, demonstrating a comprehensive and multifaceted cardioprotective profile [35, 36].

3.4 Exercise Preconditioning

Exercise preconditioning refers to the enhancement of the heart's resilience against ischemia-reperfusion (I/R) injury through consistent physical training. Exercise induces physiological and molecular adaptations in the cardiovascular system that improve its ability to tolerate ischemic stress [37]. Research has shown that exercise preconditioning confers immediate cardioprotective effects, demonstrating that even a single session can yield measurable benefits [38]. Moreover, exercise can trigger ischemic preconditioning (IP), a phenomenon in which the myocardium becomes more resistant to repeated episodes of ischemia. This process reduces infarct size during prolonged ischemia and lowers susceptibility to arrhythmias [39]. These findings underscore the crucial role of exercise in fortifying heart health and mitigating ischemic injury.

4. Discussion

During myocardial infarction (MI) and ischemia/reperfusion (I/R) injury, the interruption of blood flow deprives cardiac tissue of oxygen and nutrients, initiating a cascade of pathological events. If this deprivation persists, it can result in irreversible myocardial cell death, infarction, or even stroke. In severe cases, where the infarcted area is extensive and compensatory mechanisms fail, mortality may occur. The lack of oxygen, glucose, and fatty acids impairs mitochondrial function, triggering the excessive production of free radicals and inflammatory mediators, which compounds myocardial damage. Understanding the mechanisms underlying this injury is critical to developing effective therapeutic strategies. Exercise training has emerged as a powerful non-pharmacologic intervention capable of attenuating these damaging processes through numerous molecular and cellular pathways.

5. Conclusions

This review highlights several emerging mechanisms through which exercise promotes cardioprotection. These mechanisms involve cellular and mitochondrial membranes, brown adipose tissue, and microRNAs (miRNAs), all of which contribute to improving cardiac resilience and recovery following ischemic injury. Exercise not only reduces infarct size and inflammation but also enhances antioxidant capacity and promotes cardiac regeneration.

Given that exercise intensity appears to differentially influence these cardioprotective mechanisms, particularly in models of type 2 diabetes, future research should focus on optimizing aerobic interval training protocols. Specifically, studies should investigate how varying intensities affect the efficacy of cardioprotection, allowing for the tailoring of exercise prescriptions for individuals with cardiovascular risk factors or comorbidities.

Author Contributions

Dr. Fallahi was responsible for project development, and writing first version of paper. Dr. Shekarforoush edited the final version of paper.

Competing Interests

The authors have declared that no competing interests exist.

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