2023

Systematic review of the effect of exercise on the reduction of myocardial remodeling following a myocardial infarction compared to a sedentary approach

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Paper Submitted in Partial Fulfillment

of the Requirements for the Degree of Master of Science

in Physician Assistant Studies Augsburg University

Table of Contents

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Abstract

Background: Cardiovascular disease is one of the leading causes of morbidity and mortality in humans worldwide. Ventricular remodeling following a myocardial infarction leads to detrimental outcomes due to cardiovascular death and ventricular dysfunction. Exercise training is an adjunct strategy to reduce the myocardial remodeling process.

Purpose: The paper seeks to answer the following PICO question: P: Population with post-infarct myocardial-remodeling I: Exercise following a myocardial infarction C: Sedentary approach O: Prevention of deleterious myocardial remodeling post-MI

Methods: A comprehensive literature review was done using PubMed and Science Direct with articles published in 2019 or after. The search was conducted using the terms: myocardial remodeling exercise, post-infarct ventricular remodeling, post-infarct myocardial remodeling exercise, post-infarct myocardial remodeling, and myocardial remodeling training. Peer-reviewed articles and scholarly journals were included in the search.

Conclusions: Studies in which exercise was introduced following a myocardial infarction have demonstrated a reduction in cardiac remodeling and an improvement in overall cardiac function. These findings suggest that an exercise program following a myocardial infarction can benefit patients in reducing negative complications such as cardiac wall thinning, infarct expansion, and heart failure.

Key Words: Myocardial remodeling, exercise, myocardial infarction, training, post-infarct myocardial remodeling

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Introduction

Cardiovascular disease is one of the leading causes of morbidity and mortality in humans worldwide, causing nearly 30% of deaths around the world. [1,2] People of all socio-demographic backgrounds are affected, with a prevalence in whites (11.0%), blacks (9.7%), Hispanics (7.4%), and Asians (6.1%). [2] There is a wide range of cardiovascular diseases, including congenital heart defects, arrhythmias, coronary artery disease, heart failure, and myocardial infarction. Myocardial infarction is caused by ischemic injury due to reduced blood flow to the heart, which causes death of the cardiomyocytes through apoptosis and necrosis. [3]

In the days following a myocardial infarction, necrosis, ischemia, and loss of contractility of the myocytes result in the expansion of the infarct. [2] Acute inflammatory response following an MI is helpful in repairing the heart, but excessive inflammation may lead to ventricular remodeling. Ventricular remodeling following a myocardial infarction leads to detrimental outcomes due to cardiovascular death and ventricular dysfunction. [4–6] The remodeling can lead to cardiac wall thinning, infarct expansion and fibrosis, microvascular obstruction, functional mitral regurgitation, myocardial hemorrhage, and left ventricular dilation. [7,8]

Ventricular dilation is one of the most common causes of heart failure and is directly correlated with increased morbidity and mortality. [9,10] Majority of heart failure cases are caused by ischemic events due to partial or complete blockage of the blood flow to the heart, subsequently leading to ventricular remodeling. [2,9] The incidence of ventricular remodeling and long-term survival rate is similar in men and women who were treated with primary PCI and

proper post-MI pharmacotherapy. [11] Medical and pharmacological interventions such as reperfusion therapy and beta blockers are vital in the management of patients with occlusion of a coronary vessel to attenuate the remodeling process. Even with primary PCI and optimal pharmacological intervention, nearly half of patients demonstrate left ventricular remodeling following the infarct. [8] While long-term survival in non-remodelers and left ventricular remodelers remains the same, heart failure hospitalization rates are higher in remodelers, which indicates that strategies to prevent ventricular remodeling should be augmented. [8]

Exercise training affects the inflammatory, metabolic, and cardiovascular processes and is beneficial in reducing atherosclerotic events and improving skeletal muscle and cardiac function. [12] It is beneficial to the myocardium by improving endothelial function, increasing microvascular system development, and amplifying myocardial perfusion through vasodilation. [13] Exercise training is another adjunct strategy to reduce the myocardial remodeling process, which has been associated with improved clinical outcomes. [4,14] In the past, physical activity following a myocardial infarction was avoided but there is growing support in evidence that exercise post-MI may be beneficial. [1,12]

There is promising evidence that shows positive effects on cardiac repair in infarcted hearts, diminished apoptosis in the myocardium, and improvements in ventricular inflammation and remodeling. [1] Post-infarct aerobic exercises have been the center of many studies to reduce cardiac remodeling and improve quality of life and functional capacity. [15] These benefits are stimulated by exercise due to activation of the vascular endothelial growth factor (VEGF) dependent antigenic pathways, which are crucial in exercise-induced angiogenesis. [5]

Methods

A comprehensive literature review was done using PubMed and Science Direct with articles published in 2019 or after. The search was conducted using the terms myocardial remodeling exercise, post-infarct ventricular remodeling, post-infarct myocardial remodeling exercise, post-infarct myocardial remodeling, and myocardial remodeling training. Peer-reviewed articles and scholarly journals were included in the search. Reviews and meta-analyses were excluded from the research.

Review of Literature

Batista et al. analyzed the impact of early exercise on cardiac remodeling after myocardial infarction in rats, which was published in the *Hindawi Oxidative Medicine and Cellular Longevity* in 2020. The rodents were subjected to three months of continuous low-intensity or interval high-intensity exercises and were compared to a control sedentary group. The research looked at the ventricular geometry and hypertrophy of the heart, as well as oxidative stress, apoptosis, functional altercations, and cardiac energetic metabolism.

The data showed improvement in both low-intensity and high-intensity exercises on cardiac energetic metabolism variables compared to the sedentary group. The results also showed that continuous low-intensity exercise led to impairment of cardiac function. High-intensity interval training improved diastolic function, but early exercise did not improve systolic function, which lead to the conclusion that late physical activity protocol could be better than early exercise protocol. The researchers concluded that high-intensity interval training is the best exercise option following myocardial infarction. [4]

Garza et al. also investigated the effects of strength training and the effects on cardiac remodeling following a myocardial infarction in rats. The article was published in 2019 in *The Journal of Physiologic Sciences*, in which the animals were divided into sedentary with MI, strength training with MI, and a sham group that had no MI and no strength training. Training began 1 week after MI with animals carrying weights up a ladder for 10 weeks. The animals got an echocardiogram before the MI and after the exercise program.

The results showed that strength training reduced LV dilation and increased the thickness of viable myocardium in the systolic posterior wall. Strength training also reduced cardiac dysfunction, which was evident by the maximum rate of contraction and relaxation and improved fractional shortening. The researchers concluded that strength training was beneficial in alleviating myocardial remodeling post-infarction by improving cardiac function without causing left ventricular dilation. [7]

Liao et al. studied the effects of early moderate exercise in rats with myocardial infarction, which was published in 2019 in the *Journal of Cellular and Molecular Medicine*. The animals were divided into four groups following an induced myocardial infarction, the control sedentary group and a moderate exercise group, and a sedentary and exercise group for rats with the MI. The exercise group was trained on a treadmill every day for 2 weeks. Cardiac function and remodeling were assessed using echocardiography, histological staining, mRNA and miRNA sequencing, and real-time quantitative PCR.

The researchers found multiple significant findings. First, the results showed that early moderate exercise did not affect mortality and reduced the size of the infarct. They also saw that the cardiac function, ejection fraction, and fractional shortening significantly improved compared to the sedentary control group. Results also showed that early moderate exercise improved

angiogenesis, ventricular remodeling, and fibrosis following a myocardial infarction. There was also inhibition of the inflammatory response in the infarcted myocardium in the early moderate exercise group. Even though the ideal timing to begin an exercise program after an MI has not been established, the researchers concluded that moderate exercise 1 day after an MI and moderate exercise 5-7 days after an MI is safe. The results also concluded that early exercise beginning within 24 hours of the MI had no negative impact on rodents with a large MI. [1]

Exercise therapy coupled with stem cell therapy also showed promising results in the function of the cardiac muscle following myocardial infarction. Research published in *Sociedade Portuguesa de Cardiologia* in 2020, conducted by de Freitas et al. studied whether there is a benefit of aerobic exercise in combination with mesenchymal stem cell therapy on cardiac remodeling of the left ventricle of infarcted rats. The rats were divided into sedentary control group, sedentary with stem cell therapy, exercise without stem cell therapy, and exercise with stem cell therapy. Exercise began 24 hours after infarction for 60 minutes, 5 times per week, and lasted for 12 weeks. The results showed that the rats with exercise showed better cardiac function than the sedentary group. The researchers also found that exercise enhanced the benefits on remodeling when combined with stem cell therapy. [9]

A study conducted by Souza et al. evaluated how exercise affected the cardiac structure, functional capacity, and left ventricular function in rats with small-sized myocardial infarction. The paper was published in 2021 in Arquivos Brasileiros de Cardiologia and the researchers studied rats three months after an induced myocardial infarction. The rats were divided into three groups: the Sham group, the sedentary group with MI, and the exercise group with MI. Rats with small myocardial infarctions were included in the study, which excluded any rodents with an MI higher than 30% of the left ventricular area. The exercises were done three times per week and

lasted 12 weeks. Echocardiograms were done pre-training and post-training, gene expression was evaluated by RT-PCR, and histological studies looked at the size of the infarction.

The results showed that in rats who had an MI and were subject to exercise, the functional capacity was higher compared to the sedentary and Sham groups. Even though the infarction was below 30%, the infarcted rats still presented with increased left ventricular diameter, left ventricular mass, left atrial diameter, and systolic dysfunction. The researchers noted that the rats with MI who were in the exercise group had a higher treadmill time and distance run compared to Sham and the sedentary group and deemed exercise safe following an MI. The results showed that aerobic exercise improved functional capacity in rats with MI and the sedentary lifestyle reduced functional capacity in the Sham rats. The researchers concluded that late aerobic physical exercise reduces left ventricular geometrical changes and improved functional capacity. [15]

Another study that was looked at was written by Souza Vieira et al. and was published in the *Stem Cell Reviews and Reports* in 2020. The researchers examined whether exercise training produced cardioprotective effects on stem cells that were transplanted following a myocardial infarction. They used four groups of rats: Sham group, sedentary with induced MI, sedentary who received adipose-derived stem cells, and exercise with MI who also received adipose-derived stem cells. The rats were trained for 9 weeks before getting an induced MI and receiving stem cells. Compared to the control group, the MI caused the rats to develop myocardial hypertrophy and fibrosis, increased proinflammatory profile, and left ventricular dysfunction and dilation. The results of this study showed that exercise therapy magnified the benefits of ADSC on the infarcted myocardium and reduced cardiac remodeling post-infarction. [16]

A study written by Shahi et al. and published in 2020 in *Open Medicine* also looked at the effects of voluntary exercise on cardiac remodeling following a myocardial infarction in mice. They too had four groups of mice: sedentary Sham, sedentary MI, exercise sham, and exercise MI. After getting an induced MI, the sedentary group was under usual care while the exercise group received a running wheel and were allowed to engage in voluntary running immediately following the MI for 28 days. Baseline echocardiographs were done and then repeated 28 days afterward, which measured the left ventricular wall thickness, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, the ejection fraction, and the fractional shortening percentages. Heart tissue was also histologically examined and examined with immunohistochemistry to assess the infarct size and the morphology of the infarcted size. RNA extraction, quantitative RT-PCR, measurements of plasma levels of cytokines, and immunoblotting were also performed.

The results indicated that exercise improved cardiac remodeling, suppressed myocardial inflammation, reduced cardiac fibrosis, and improved mitochondrial function. The researchers state that exercise can stimulate protective reactions against permanent tissue damage produced in the myocardium by ischemia. The results also showed that the body weights were significantly lower in the exercise groups compared to the sedentary groups, but voluntary exercise did not significantly affect the survival rate. The researchers concluded that voluntary exercise following an MI can be beneficial to attenuate cardiac remodeling through inflammatory modulation. [17]

Another study that provided promising evidence was published in 2020 in Biomedicine and Pharmacotherapy by Wang et al. The researchers looked at the cardiac function and structure following high-intensity interval training in rats with acute MI. The rats were divided into four groups: Sham, sedentary MI, moderate-intensity continuous training, and high-intensity

continuous training. The training began 1 week following the MI and studies were done at 4 and 8 weeks. The cardiac functions were examined by echocardiography and hemodynamic measurements. The changes in infarct size, angiogenesis, myofibroblasts, collagen accumulation, inflammation level, and endothelin and renin-angiotensin-aldosterone system activities were recorded as well.

The results showed that the function and structure of the heart following an MI deteriorated significantly but 8 weeks of high-intensity interval training significantly improved those outcomes. High-intensity interval training enhanced left ventricular systolic pressure and improved left ventricular end-diastolic pressure and maximum peak relaxation velocities. It also helped to maintain cardiac function, increased angiogenesis, decreased collagen and fibrosis collection, and reduced the infarct size. The researchers concluded that a high-intensity interval training program could reverse left ventricular remodeling and have a beneficial role in the repair of cardiac muscle due to a possible connection with the induction of inflammation and suppression of activities of endothelin and the renin-angiotensin-aldosterone system. [12]

While the results in studies using animal subjects do not directly correlate to effectiveness in human patients, they provide a good indication that post-infarct exercise programs may be beneficial to reduce adverse effects in humans. The study done by Kasperowicz et al. shows that cardiac exercise rehabilitation was beneficial in increasing exercise capacity in patients' post-infarct. Published in 2019 in *International Journal of Environmental Research and Public Health*, the retrospective chart review looked at 100 patients who received complete revascularization at Lubuskie Pulmonology and Cardiology Hospital. The subjects were aged 40-75, had BMI under 40, had controlled arterial hypertension, no anemia, no pulmonary comorbidities, and were hospitalized for a minimum of 3 weeks with exercise EKG test, or 6 min

walk test performed at least prior to and after rehabilitation. The patients were grouped according to gender, age below or above 55, BMI below or above 25, EF under 40%, 40%-49%, and above 50%, concomitant diabetes or nicotine dependence.

The results showed that all patients who underwent a cardiac rehabilitation program had a significant exercise capacity increase. The most beneficial effects were seen in groups of patients who were older than 55, males, and nicotine-dependents. [13]

Discussion

Patients who had a myocardial infarction often suffer from reduced ejection fraction due to myocardial remodeling. When early remodeling is mitigated or reversed, patients suffer significantly lower rates of adverse incidents in the first year following the infarction. [14] All of the studies found in the last five years have found that exercise following a myocardial infarction has beneficial effects on reducing the adverse consequences of myocardial remodeling.

While there still needs to be research done to create an optimal exercise program for humans to maximize the benefits of exercise, the current literature shows that exercise has benefits over sedentary approaches. Batista et al. and Wang et al. showed that high-intensity interval training is the best option following a myocardial infarction compared to low-intensity continuous training and Liao et al. showed that moderate exercise was also safe. [1,4,12] The study by Souza et al. also showed that late aerobic exercise was beneficial in reducing left ventricular geometric changes and improving functional capacity.[15] These results are confirmed by the study by Garza et al. as well, in which they found that exercise training reduced left ventricular dilation and improved cardiac function by reducing myocardial remodeling. [7] Attenuation of myocardial

remodeling was witnessed by Shahi et al. as well, in which the results indicated that inflammatory modulation due to exercise was a factor in improving cardiac function. [17]

Since most of these studies have been conducted using rats, the results may not directly correlate to human patients. Due to overwhelming evidence of exercise benefits post-infarct in animal studies, a study with human subjects would be very advantageous to see how well exercise alleviates cardiac remodeling.

The proposed study would examine 3 groups of patients following a sedentary, moderate-intensity interval exercise, and high-intensity interval exercise programs for 12 weeks after 1 week of rest following the myocardial infarction. Baseline echocardiographs would be done, another one halfway through training, and a third measurement once the training has been finished. Hemodynamic measurements and functional and exercise capacity would be monitored as well. Patient consent would obviously be required to participate and withdrawal from the study will be permitted and noted in the final results.

Conclusion

This systematic review examined the effect of exercise on the reduction of myocardial remodeling following a myocardial infarction compared to a sedentary approach. The following PICO question was asked:

P: Population with post-infarct myocardial remodeling

I: Exercise following a myocardial infarction.

C: Sedentary approach

O: Prevention of deleterious myocardial remodeling post-MI

Studies in which exercise was introduced following a myocardial infarction have demonstrated a reduction in cardiac remodeling and an improvement in overall cardiac function. These findings suggest that an exercise program following a myocardial infarction can benefit patients by reducing negative complications such as cardiac wall thinning, infarct expansion, and heart failure.

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