REVIEW PAPER

CARDIOPROTECTIVE EFFECTS OF PHYSICAL ACTIVITY: FOCUS ON ISCHEMIA AND REPERFUSION

Milos Glisic[1*], Bozidar Pindovic[2*]

[1] *University of Kragujevac, Faculty of Medical Sciences, Department of Physiology, Kragujevac, Serbia*
[2] *University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacy, Kragujevac, Serbia*

* Milos Glisic and Bozidar Pindovic contributed equally (50 % each) to this work, and both should be considered first authors.

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Corresponding author:

Bozidar Pindovic,

University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacy,
Svetozara Markovica 69, 34000 Kragujevac, Serbia

Phone: +381 65 33 76 999

E-mail: pindovic.bozidar@gmail.com

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ABSTRACT

This review aimed to revisit the old and introduce some of the new various cardioprotective effects of physical exercise, focusing on ischemia-reperfusion injury. A wealth of data shows that regular physical exercise is necessary to prevent cardiovascular diseases. In the last few years, a number of new training regimes, usually modified variations of high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) protocols, have been rising in popularity among people of all ages. Since exercising is not limited to only healthy people, our study emphasized the benefits of HIIT and MICT in preventing or mitigating cardiac ischemia-reperfusion injury. Different kinds of research are being performed, studying the various positive and side effects of these training regimes, all in hopes of finding the most optimal ones. So far, all of them have shown that exercising to any extent, even for a short period of time, is beneficial in one way or another, and outweighs the possible risks it might have. We also revisited some of the known molecular mechanisms responsible for many of the effects of physical exercise and introduced some new findings related to them. Lastly, we summarized and compared the benefits of different HIIT and MICT protocols to narrow down the search for the most efficient training method.

Keywords: *HIIT and MICT, cardioprotection, exercise, ischemia-reperfusion injury.*

INTRODUCTION

Data from the World Health Organization (WHO) shows that about 17 million people worldwide die from cardiovascular diseases each year, with ischemic heart disease being the most common cause of death in Europe (1). At the cellular level, the dominant mechanism of myocardial ischemia is the so-called ischemic/reperfusion injury (I/R) involving molecular, biochemical, metabolic, functional, and morphological damages of cardiomyocytes, which occur both during ischemia and reperfusion (2). These damages may, in turn, lead to cell death (2).

In recent decades, treatment and therapy of ischemic heart disease have been among the greatest tasks put before health communities worldwide. An additional concern for these patients is the pharmacological approach and the development of many efficient pharmacological agents to control and treat this disease (1-3). Besides the therapeutic problem, it is well known that the prevention of a possible ischemic event can be an important factor in reducing the consequences of this disease both in terms of the severity of the clinical picture and treatment costs. Therefore, in order to prevent myocardial infarction from I/R damage, a preconditioning procedure has been developed. Preconditioning is a procedure for protecting and preventing myocardium from ongoing ischemic and reperfusion damage, carried out by pharmacological and non-pharmacological principles (4). Despite the significant progress in this field, it has been noticed that pharmacological preconditioning is increasingly associated with numerous side effects resulting in a financial burden on the system and the individual. This has led researchers and doctors to find new solutions to the aforementioned issues.

In recent years, the development of new non-pharmacological principles of preconditioning has become one of the leading research tasks in this field of investigation. Out of the known non-pharmacological types of preconditioning, physical activity has proven to be potentially the most effective, with several promising results in this field. This claim has been confirmed by numerous epidemiological studies indicating the cardioprotective effects of regular exercise (5, 6). It has been observed that the frequency of myocardial infarction is reduced in physically active individuals (5).

Interestingly, the positive effects of preconditioning with exercise are not limited to the exercise period alone, as there is evidence that the protective effects remain for (up to) 9 days after exercising (5). However, studies examining the effects of exercise on I/R have yielded ambiguous results, with some researchers reporting that training improves myocardial tolerance to I/R (5), while others state that there is no improvement or even reduced myocardial tolerance I/R (7). In addition to these inconsistent results, another issue is that it is unknown which type of physical activity or training (aerobic or anaerobic) achieves the best results in preconditioning of I/R.

Therefore, defining a specific training protocol would contribute to an additional and vital clarification of this issue. Although specific protective mechanisms of exercise preconditioning have not been identified so far, it is assumed that they include an increase in myocardial enzymatic antioxidant activity and more successful neutralization of reactive oxygen species, especially during the reperfusion period (5, 6). In the last two decades, there has been a significant rise in a plethora of data regarding the cardioprotective impact of physical activity, with a bulk of different kinds of evidence steaming from animal and human models. However, among all the conclusions, one thing is certain: literature data is strongly inconsistent, leaving us still with many open questions.

For our review we used the PubMed database, focusing mostly on articles published in the last 5 years - if possible, but depending on the information needed, older ones have also been reviewed. In the filter section, all types of available articles were selected, then the search has been narrowed down mostly using keywords cited in the abstract. The search started with approximately 84000 studies when searching for ischemia-reperfusion, for it to be narrowed down to less than 170 by adding other keywords.

THE CONCEPT OF ISCHEMIA-REPERFUSION INJURY - NEW INSIGHTS

Myocardial infarction is considered an irreversible state, most of the time an end-phenomenon following prolonged myocardial ischemia. Ischemia itself is defined by low blood flow through the coronary vessels, caused by a plethora of reasons, which leads to less blood arriving at the heart and thereby delivering a mostly insufficient amount of nutrients for cardiomyocytes, leading to necrosis of the myocardial tissue and the cells themselves (8). Moreover, while significant advances have been made in treating myocardial ischemia over the past decade, timely reperfusion is still considered by many as one of the best methods, if not the best, in salvaging the myocardial tissue (9). Nonetheless, it is far from perfect, and as many clinical observations and trials showed, additional cardioprotection is necessary to reduce the mortality rate of said injuries. Since infarction size is considered one of the predominating factors for predicting the life span of patients suffering from myocardial infarction, many cardioprotective measures aim to reduce the size of said injury in patients (9).

The classic paradigm of cardioprotection, which refers to reducing the infarct size caused by sustained coronary occlusion and reperfusion via applying several cycles of brief coronary occlusion and reperfusion, is the leading theory in modern life cardio-therapy (10). Despite this, there exists a gap between a significant number of preclinical studies where an effective reduction of infarct size has been achieved by either mechanical or pharmacological interventions and

their translation into a clinical benefit in patients with acute myocardial infarction (7-10).

Since, in most cases, it was not possible to apply preconditioning in patients with acute myocardial infarction, due to the event timing being unpredictable and the fact that most of the methods provided a relatively short window of protection, some other approaches were considered to be implemented in reducing the damage caused by prolonged ischemia (10).

Vinten-Johansen and others have shown that it is also possible to reduce infarct size with ischemic postconditioning to almost the same extent as preconditioning (9). The third method of cardioprotection, which was first regarded as just something possible in a laboratory, but has gained traction in recent times thanks to its translation into clinical practice, is remote ischemic preconditioning (12). As helpful as these methods have proven to be, they still rely on inducing ischemia/reperfusion, still causing injury to a degree.

New research done in recent years has provided us with many insights about many different mediators, both into those responsible for and those present during myocardial infarction. Some of the newer findings show that many different molecules like receptor-dependent triggers or cytosolic mediators have a lot more impact on ischemia processes than previously thought (13-15). That led to many new ongoing research projects focusing on studying these molecules and their interactions, opening the way to new possible ischemia treatments.

This is why a better understanding of signal transduction is considered necessary to induce cardioprotection without causing any form of injury to any tissue. Many studies have reported over 100 different signaling molecules and mechanisms taking part in conditioning (13-18).

One thing hypothesized in most of them is the existence of a trigger molecule released during the conditioning that acts as a stimulus for activating the cardioprotective mechanisms during sustained ischemia, which as a result, has an attenuated injury compared to an ordinarily irreversible one. The specific trigger has not yet been identified, but a number of both physical and chemical stimuli are in the process of examining their influence on cardioprotection (16). Although not proven in conditioning models, even mild hypothermia protects the heart cells during ischemia by slowing their metabolism and activating extracellular regulated kinases while also regulating heat shock proteins (17). Some endogenously released molecules like calcium ions, or reactive oxygen species (ROS), reactive nitrogen species also have a role in cardioprotection. ROS, in particular, have an ambivalent role – their excess propagates irreversible injuries, while in small concentrations, they protect cytosolic kinases, increasing protection. Reactive nitrogen species also show dose-dependent traits like ROS (20).

Intracellular calcium overload, rapid pH normalization after reperfusion, and oxidative stress result in mitochondrial permeability transient pore (MPTP) opening, which causes cell death.

Proliferator-activated receptors (PPARs), a family of nuclear receptors that act as ligand-induced transcription factors, also exhibit pleiotropic cardioprotective properties. In addition to being the primary transcriptional regulators of myocardial lipid metabolism and energy homeostasis, PPARs also exhibit antioxidant and anti-inflammatory properties.

Activation of PPARb/d suppresses ROS generation in cardiac myocytes of adult rats subjected to oxidative stress, implying enhanced catalase regulation. Furthermore, deletion of cardiac PPARb /d in mice resulted in decreased bioenergy, cardiac hypertrophy, and congestive heart failure, while PPARb/d was also shown to be essential for the adult heart to maintain mitochondrial capacity and oxidative metabolism (21).

Cell destruction via programmed cell death - such as apoptosis, autophagy, necroptosis, and pyroptosis occurs in controlled physiological or in some pathological conditions. For example, when an I/R injury occurs, there is an increase in free oxygen radicals and calcium, which leads to the death of a large number of myocardial cells and the release of harmful molecules like DAMP (Damage-associated molecular patterns), which then trigger inflammatory cells to clear debris from the pathway, causing an even greater number of myocardial cell deaths.

DAMP releases cytosolic multiprotein oligomers from host cells called inflammation mediators such as macrophages that secrete pro-inflammatory cytokines IL-1beta and IL-18 (interleukins) together with gasdermin D, which induce programmed pyroptosis-type cell death (22).

During myocardial reperfusion, fatty acid oxidation (FA) recovers rapidly as a significant energy source while reducing glucose oxidation, which produces detrimental effects on postischemic functional recovery. In addition, an in vitro study has shown that stimulation of glucose metabolism inhibits apoptosis in neurons, cancer cells, and leukemic T cells. However, whether glucose uptake changes and contributes to IPC (ischemic preconditioning) cardioprotection during reperfusion remains unknown (23).

Some other mechanisms contributing to cardiomyocyte necrosis during ischemia are failure of ion pumps (as a result of reduced free energy change of ATP- hydrolysis in the absence of oxygen), acidosis, and Ca2+ overload.

During early reperfusion, when ATP (adenosine triphosphate) formation recovers, myofibrillar contraction is excessive and uncoordinated in response to increased Ca2+ cycling between the sarcoplasmic reticulum and the cytosol (24). Calcium ions have not shown many effects during conditioning, notably only adenosine and PKC (Protein kinase C)

activation. Many neurotransmitters and hormones, such as acetylcholine, angiotensin, catecholamines, can trigger cardioprotection mechanisms through activating their corresponding receptors, out of whom only α-adrenoreceptors have direct involvement in conditioning by forming adenosine and activating PKC in IPC (25).

Recently, many regulated forms of cardiomyocyte cell death have been recognized as an essential part of ischemia-reperfusion injuries, including apoptosis, necroptosis, autophagy, and ferroptosis. Cardiomyocyte apoptosis occurs either in response to DNA damage and increased ROS and cytosolic Ca2+ levels or due to the activation of sarcolemmal death receptors.

Apoptosis is an energy-requiring process involving the release of cytochrome C from mitochondria and the activation of caspases resulting in DNA fragmentation.

With the activation of sarcolemmal tumor necrosis factor (TNF) receptors or Toll-like receptors, necroptosis occurs, leading to the formation of the necrosome and, with the help of different kinases, also induces pore formation in the sarcolemma (26-28).

Another type of regulated cell death happening during or after ischemia is ferroptosis. It is characterized by lipid peroxidation and cell membrane destruction (29).

Usually occurring during an imbalance of pro and antioxidative molecules, it is linked to three different but interconnected pathways - one regulated by transporter molecules, one by enzymes, and one inducing lipid peroxidation (30). The transporter-regulated pathway induces ferroptosis by inhibiting system xc- an amino acid membrane transporter necessary for glutathione (GSH) synthesis (29). Since GSH is a mandatory cofactor for the proper functioning of GPX4 - an enzyme that transforms the toxic lipid hydroperoxide into less toxic alcohols, it can also be considered a part of the second enzyme-regulated pathway.

Other iron-containing enzymes, e.g., ALOX (arachidonate lipoxygenase) or the NADPH oxidase (NOX) family of enzymes, also play a critical role in starting and propagating the peroxidation of fatty acids. The third lipid peroxidation inducing pathway involves the oxidation of both poly- and monosaturated fatty acids and their metabolites. Said oxidation happens when excess ROS, usually originating from mitochondria or NADPH oxidase, among other molecules, damage the lipids in cells, thereby triggering peroxidation (31).

Growth factors, such as insulin-like growth factor 1, fibroblast growth factor 1, and fibroblast growth factor 2, have been proven to reduce ischemia after administration (32). Cytokines/chemokines have a more causal role in IPC and POC. Tumor necrosis factor α (TNFα) is mandatory for IPC and postconditioning (POC) and reduces IS on exogenous administration. The entire process is mediated by activating TNF receptor 2, STAT 3, and mitochondrial KATP-channels. Interleukin 6 and 10 followed by subsequent signaling are necessary for IPC and Remote ischaemic preconditioning (RIPC) (32-35).

The transfer of cardioprotective signals from peripheral organs (brain, mesentery, kidney, skeletal muscles, skin) to the heart is the result of a complex neurohumoral interaction. Ischemia/reperfusion, trauma, or even induced activation of sensory fibers in the peripheral organs, release an as of yet unidentified humoral factor through the central nervous system (33).

In some studies, activation of the autonomic nervous system was considered mandatory to reduce IS in the ischemic/reperfused myocardium, while in others, it was not (34). Transferring factors of protection – namely humoral via plasma or dialysates obtained after peripheral preconditioning cycles from one individual or individual's heart to another's, even across species, has been shown as possible (36).

Apart from cardiomyocyte cell death, each ischemia-reperfusion cycle is followed by significant and partly irreversible injuries of microvascular cells. The most severe form is defined with the destruction of capillaries resulting in a no-reflow phenomenon (37). Coronary atherosclerosis with erosion or plaque rupture is an initiator of myocardial infarction that also affects coronary microcirculation. Dislodged debris from the ruptured epicardial plaque is sent into the bloodstream, usually causing microembolization. Plaque rupture or erosion is usually followed by the release of pro-inflammatory factors, vasoconstrictor, and pro-thrombotic factors (37, 38). Ischemia-reperfusion can also cause vasomotion to be impaired by endothelial and vascular smooth muscle cell dysfunction (39). Many different aggregates (platelets, leukocytes, and erythrocytes) obstruct coronary circulation. Increased permeability of capillaries is a significant factor contributing to interstitial edema (37).

THE POSITIVE EFFECTS OF PHYSICAL ACTIVITY ON THE CARDIOVASCULAR SYSTEM

Cardiovascular diseases (CVDs) such as heart ischemic or coronary artery disease (CAD) continue to be one of the major causes of death worldwide. Genetic features combined with age and other factors such as dyslipidemia, atherosclerosis, and hypertension are considered risk factors (RF) for developing CVDs. Furthermore, the severity of these diseases is also significantly impacted by excess caloric intake and a lack of physical activity (39).

Numerous studies published in the last decade also support the statement that regular physical exercise represents an effective and long-term cardioprotective mechanism. Other studies also debate the fact that exercising regularly reduces a significant number of cardiovascular (CV) RF like hypertension, obesity, diabetes mellitus, and many others (40).

While the exact mechanisms are not yet fully known, some studies have clarified that total energy expenditure during exercise, and exercise intensity play a significant role in preventing myocardial infarction (MI) (40, 41). Therefore, numerous new training protocols were conceived and tested recently, pushing the boundaries of what was previously thought to be a healthy habit to a therapeutic method applicable in many different areas followed by promising results. Specific strategies promoting cardiac adaptations as non-pharmacological ways to mitigate the risks of CV events have been rising in the past few years.

Vigorous training exercises prior to ischemic events could prevent lethal myocardial injury, which cardiac preconditioning supports (41). Another effect of physical exercise is induced autophagy in cells – including cardiomyocytes. Autophagy is an essential cellular process with the purpose of maintaining energy homeostasis - which in turn serves as a protection mechanism for cells.

Some published papers have shown that autophagy can not only be induced but also stimulated via controlled ischemia preconditioning (42). Different kinds of short and long-term exercises, repeated during a period of time, could also be the initiators for stress conditions leading to autophagy in cardiomyocytes. A great number of theories argue that autophagy is, in fact, what allows the heart to stay protected during high-intensity exercises for extended periods of time (43, 44).

Evidence supports a strong correlation between vascular function and cardiorespiratory fitness (44). Preserved vascular function is necessary for stopping the progression of the atherosclerotic cascade, thereby significantly decreasing susceptibility to all kinds of CV events, including MI and strokes (45). Since both high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) have been shown to be successful in improving cardiorespiratory fitness, many studies today are trying to compare the two, with the end goal being the identification of both their separate and combined impact on vascular function (46). Randomized trials studying HIIT practice for extended time periods presented results showing greater effects in reducing RF for CVDs compared to MICT (47, 49). Even diastolic and systolic blood pressure values were significantly lower after HIIT protocols than after MICT protocols. They also showed that HIIT significantly improved brachial flow-mediated dilatation compared to MICT (48).

Papers presenting studies conducted on heart failure patients have shown that HIIT induces significant enhancement in antioxidant status compared to MICT (48). There are studies showing a significantly greater increase in bioavailability of NO following HIIT than a MICT protocol (50). After 12 weeks of HIIT, insulin sensitivity (results obtained via HOMA-IR (Homeostatic Model Assessment for Insulin Resistance)) improved faster than after MICT in DM type 2 patients. Both protocols led to a significant reduction in body fat percentage with no significant difference between them (51-53).

Although regular physical activity has been proven to reduce CVD-associated morbidity and mortality, the optimal duration, frequency, and intensity remain unclear (54). Research on a great number of animal models is being conducted to determine molecular mechanisms related to the cardioprotective effects of exercise (55). A review paper recently published presented that long-term MICT prevents cardiac injury while also having long-term system-wide protective effects (56). It also significantly reduced the infarction size following myocardial ischemia. Short-term exercise can mimic ischemic preconditioning, thereby offering innovative ways to investigate molecular mechanisms of exercises that promote cardioprotection (55, 56).

Conducted on Wistar Albino rats, a study has shown that HIIT promotes hypertrophy of cardiomyocytes and interstitial fibrosis while modulating apoptosis signaling pathways in healthy rat myocardium (57). Combining HIIT with intermittent fasting was also shown to reduce pro-apoptotic and increase antiapoptotic signaling while mediating and reducing potential fibrosis and hypertrophy caused by HIIT protocols (56, 57).

Experimental studies on healthy rodents have shown that HIIT could increase cardiomyocyte length, width and volume, and both right and left ventricles' mass while preserving left ventricular function (58-60). Experimental cardiac injury studies using HIIT protocols on rats have shown reduced ventricular hypertrophy and fibrosis, improved cardiac function, and reduced apoptosis of myocardial cells (58-60). Other studies - namely a hypertension model, showed that HIIT could increase left ventricular mass without significant fibrosis, suggesting that the effects of HIIT on myocardium may produce different results depending on the experimental model used (58-60).

Other studies examining the effect of exercise training on the activity of various glycolytic enzymes and transporter proteins found that their capacity is either mildly increased or does not change at all no matter what training protocol is used (54). Palmitate oxidation rates were significantly increased in trained hearts before and after ischemia (54). A known fact is that high levels of plasma-free fatty acids observed after acute myocardial ischemia are detrimental to the heart during reperfusion. Increased levels of fatty acid oxidation found in hearts taken from rats that underwent a training protocol are associated with higher survival rates after ischemia, which supports the idea that increased fatty acid oxidation protects these hearts from the toxic metabolic effects of fatty acids after ischemia (61).

In summary, numerous studies published in the last decade support the statement that regular physical exercise is an effective and long-term cardioprotective maneuver. Other studies also debate the fact that exercising regularly reduces a significant number of cardiovascular risk factors like

hypertension, obesity, diabetes mellitus, and many others. The mechanisms responsible need to be studied more while considering the energy required for them in order to finally complete the transition from animal models to clinical studies.

CARDIOPROTECTIVE EFFECTS OF PHYSICAL ACTIVITY ON ISCHEMIA-REPERFUSION INJURIES

Numerous studies have reported regular exercise to induce autophagy. It is hypothesized that exercise preconditioning related to autophagy in cardiomyocytes results from intermittent ischemia–hypoxia cycles. Induced in said manner, it allows the heart to stay protected for subsequent high-intensity exercises (62). Autophagy as a cellular process maintains energy homeostasis, thereby acting as a protection mechanism.

Studies have shown that autophagy can be induced in ischemic or hypoxic heart tissue during and by various stress conditions. Exercise preconditioning, consisting of short-term and long-term repeated intermittent exercise, can reduce myocardial injury caused by exhaustive, continuous high-intensity exercise (63).

High-intensity exercise can pose a risk to myocardial health, as it inevitably results in an imbalance between increased oxygen consumption and insufficient oxygen uptake. Repeating short-term, intermittent exercises could improve the adaptation rate of myocardial cells and their tolerance of stress, establishing stronger protection against excessive ischemia–hypoxia caused by continuous high-intensity exercise (64). Ischemic preconditioning, also known as intermittent ischemia/reperfusion (I/R), can result in increased cardioprotection, thereby alleviating subsequent ischemia–hypoxia-like injuries or infarction (63, 64).

Exercise preconditioning significantly suppresses high-intensity exercise-induced myocardial injury and ischemia–hypoxia in both early and late cardioprotection. A relatively clear correlation between autophagy and exercise-induced ischemia–hypoxia has been proven in numerous studies. In comparison, while both high-intensity exercise-induced and preconditioning-induced ischemia–hypoxia result in the induction of autophagy, high-intensity exercise-induced autophagy has been shown as less efficient (65).

One of the consequences of acute MI (AMI), along with ischemia, is the increase of reactive oxygen species (ROS) and resulting in oxidative stress (66). The loss of cardiomyocytes causes the subsequent impairment of heart function. Cellular metabolic homeostasis is maintained in physiological conditions by balancing ROS production and antioxidant defense (known as REDOX state) (67). Before ischemia, a disturbance in said balance contributes to the development of coronary artery disease. Therefore it is hypothesized that physical training may have a protective effect on ischemic conditions by strengthening antioxidant tissue responses (68).

Regular, aerobic physical exercise has been shown to enhance the metabolic activity of active muscles, their mitochondrial function, ATP production, and hence, ROS production. Therefore, by activating several different antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and non-enzymatic antioxidants, such as glutathione and vitamin E, higher ROS production may directly fasten muscle adaptation to various stress conditions (69). Considering the role of ROS in the loss of heart function induced by AMI, preventive physical training may provide a cardioprotective effect against myocardial infarction injury by promoting antioxidant responses. Beneficial effects of aerobic training performed after AMI have been demonstrated for the recovery of cardiac function (70). Experimental studies have shown a positive effect of aerobic training prior to myocardial infarction on ventricular function and infarction size (71).

However, no concrete evidence on antioxidant responses in the myocardium as a protective factor promoted by physical training performed before AMI has been presented as of yet (72). Similar to ischemic preconditioning, high-intensity exercise has been shown to decrease myocardial infarction size (73). Some studies have shown that endurance exercise training has positively impacted heart survivability through beneficial hypertrophy, angiogenesis, and improved contractility.

Additionally, individuals who exercise regularly tend to experience relative bradycardia due to autonomic modulation, allowing for extended diastolic periods and elevated myocardial perfusion at submaximal workloads. Although the mechanism is not fully understood, there is evidence to suggest that exercise may mimic the favorable, cardioprotective effects of ischemic preconditioning and attenuate cardiomyocyte death in the setting of myocardial ischemia-reperfusion (I/R) (74). Controversy is present in literature, taking the intensity of exercise and the level of cardioprotection into account. An earlier study comparing moderate- and high-intensity exercise in rats showed equivalent protection against I/R injury (31).

To summarize, physical activity has been proven to positively affect ischemia-reperfusion injuries in the context of mediating and lowering the permanent damage done by them or helping by inducing a faster and better recovery process.

CONCLUSIONS

Numerous studies published in the last decade support the statement that regular physical exercise is an effective and long-term cardioprotective maneuver. While the exact mechanisms are not yet fully known, some studies have clarified that total energy expenditure during exercise and exercise intensity plays a significant role in preventing myocardial infarction. According to available data, both HIIT and MICT

protocols provide cardioprotection. Even though they activate more or less the exact mechanisms, some of them are more prominent when induced by one kind of exercise than the other. While the optimal intensity threshold has not yet been determined for I/R protection, so far, it appears that greater intensity overall is more beneficial in long-term exercise regimens. In our opinion, for pushing promising scientific evidence forward to clinical practice, future investigations and studies should consist of both a pre-clinical and clinical part. Although exercise based cardioprotecton maneuvers have been proven to be beneficial in I/R, some future studies may imply the estimation of a more individualized approach to both HIIT and MICT.

Table 1. Summary of exercise-induced cardioprotection of ischemia-reperfusion injuries

Author	Year of publication	Study model	Type of exercise	General mechanisms
Deutsch E et al	1990.	Human	HIIT/MICT	Vascular adaptation
Liu Y et al.	1995.	Animal	HIIT/MICT	Enzyme activation
Jenkins DP et al.	1997.	Human	HIIT/MICT	Reducition of risk factors
Thuny F et al.	2012.	Human	HIIT/MICT	System-wide adaptation
Buscemi S et al.	2013.	Human	HIIT/MICT	Antioxidative
Weston KS et al.	2014.	Human	HIIT	Energy regulation, Antiinflamation
Mitranun W et al.	2014.	Human	HIIT/MICT	System-wide adaptation
Vujic A et al.	2018.	Animal	HIIT/MICT	Signaling modulation, Heart adaptation
Rossello X et al.	2018.	Human	HIIT/MICT	Autophagy
Moller AB et al.	2019.	Human	HIIT/MICT	Heart adaptation, Vascular adaptation
Papatheodorou I et al.	2021.	Animal	HIIT/MICT	Antioxidative

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