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Effects of physical exercise on the prevention and treatment of ischemia injuries: a literature review

Efeitos do exercício físico na prevenção e tratamento de lesões por isquemia: uma revisão de literatura

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ABSTRACT: *Introduction*: In 2013, more than 17.3 million deaths / year were caused by cardiovascular diseases, accompanied by an estimate of more than 23.6 million deaths by 2030, registering the largest global cause of death. *Objective*: This literature review aims to systematize knowledge about the effects of physical exercise such as measuring and / or treating injuries caused by ischemia, in order to instigate new research and contribute to the dissemination of current information. *Methodology*: This study analyzed a bibliographic review of an analytical nature of the studies and respect for the effects of physical exercise, as a treatment and treatment measure for injuries caused by ischemia in tissues of scientific experimentation animals, in which 99 articles were collected from a search in the Pubmed, SciELO and Lilacs databases with the descriptors: "ischemia", "exercise", "mice" and "muscle". *Results and Conclusio*n: The current literature points to a consensus on the cardioprotective and neuroprotective effects of physical exercise, with increased resistance against oxidants, improvement in the angiogenesis process, greater resistance against acidification of the environment, improvement in the cardiomyogenesis process, and presents as molecular signaling pathways that can explain the advanced effects of physical exercise in its different intensities.

Keywords: Ischemia; Exercise; Oxidative stress.

RESUMO: *Introdução*: Em 2013 mais de 17,3 milhões de mortes/ano foram causadas por doenças cardiovasculares, acompanhado de uma estimativa de mais de 23,6 milhões de mortes para 2030, representando a maior causa global de morte. *Objetivo*: Esta revisão de literatura tem como objetivo a sistematização do conhecimento acerca dos efeitos do exercício físico como medida de prevenção e/ou tratamento em lesões causadas por isquemia, a fim de instigar novas pesquisas e contribuir para a disseminação de informação atual. *Metodologia*: Este estudo constitui uma revisão bibliográfica de caráter analítico dos estudos a respeito dos efeitos do exercício físico como medida de prevenção e tratamento de lesões causados por isquemia nos tecidos de animais submetidos a experimentação científica, em que foram coletados 99 artigos a partir de uma busca nas bases de dados Pubmed, SciELO e Lilacs com os descritores: "ischemia", "exercise", "rats" e "muscle". *Resultados e Conclusão*: A atual literatura aponta para um consenso acerca dos efeitos cardioprotetores e neuroprotetores do atividade física, com ênfase no aumento da resistência contra agentes oxidantes, melhoria no processo de angiogênese, maior resistência contra acidificação do meio, melhoria no processo de cardiomiogênese, e apresenta as vias de sinalização moleculares que possivelmente explicam os efeitos advindos do exercício físico nas suas mais diferentes intensidades.

Descritores: Isquemia; Exercício físico; Estresse oxidativo.

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INTRODUCTION

In 2013, more than 17.3 million deaths/year were caused by cardiovascular diseases, accompanied by an estimate of more than 23.6 million deaths by 2030, representing the largest global cause of death[1]. In order to significantly reduce the possible adverse consequences of cardiovascular disease (CVD), in 2011, the United Nations officially defined non-communicable diseases as the main concern for global health[2].

In this sense, physical exercise, when it is an integral part of labor activities and leisure, has the beneficial effects of preventing coronary heart disease and reducing mortality from all causes, as clearly indicated by epidemiological data[3,4,5]. Thus, it's evident the relevance of studies in this area to understand how physical activity acts on the human body to obtain these benefits.

Furthermore, the advantages of physical exercise practiced before cerebral ischemia were indicated by several studies, denoting a neuroprotective effect on the brain, in addition to benefits on motor performance[6,7,8]. Angiogenesis in ischemic hearts is also improved when training is used as a treatment, on treadmills, for example, it was able to produce significant improvement in collateral vessel growth in patients with coronary artery disease.

Therefore, this literature review aims to systematize knowledge about the effects of physical activity as a preventive and / or treatment measure in injuries caused by ischemia, in order to instigate new research and contribute to the dissemination of current information.

METHODS

This study constitutes an analytical bibliographic review of the studies regarding the effects of physical exercise as a measure of prevention and treatment of injuries caused by ischemia in the tissues of animals submitted to scientific experimentation.

Data collection was carried out on January 5, 2020, and the National Library of Medicine (PUBMED), Scientific Eletronic Library Online (SciELO) and Latin American and Caribbean Literature in Health Sciences (LILACS) databases were used for the research.

It was defined as an inclusion criterion: articles published from 2015 until the date of data collection, in order to select current information on the subject. Another criterion concerns the descriptors used. This study included articles found in the search for descriptors "ischemia", "exercise", "rats" and "muscle".

After selecting the articles according to the inclusion criteria previously defined, were followed steps, in that order: exploratory reading; selective reading and choice of material that fit the objectives and theme of this study; analytical reading and analysis of the texts, ending with the performance of interpretive reading and writing. Criteria based on Jadad Scale, score by Pedro or quality of research were not used. All articles found were evaluated by the five authors responsible for writing this study. Only articles available in English or Portuguese were included in the results of this study. The following flowchart details the article selection process.

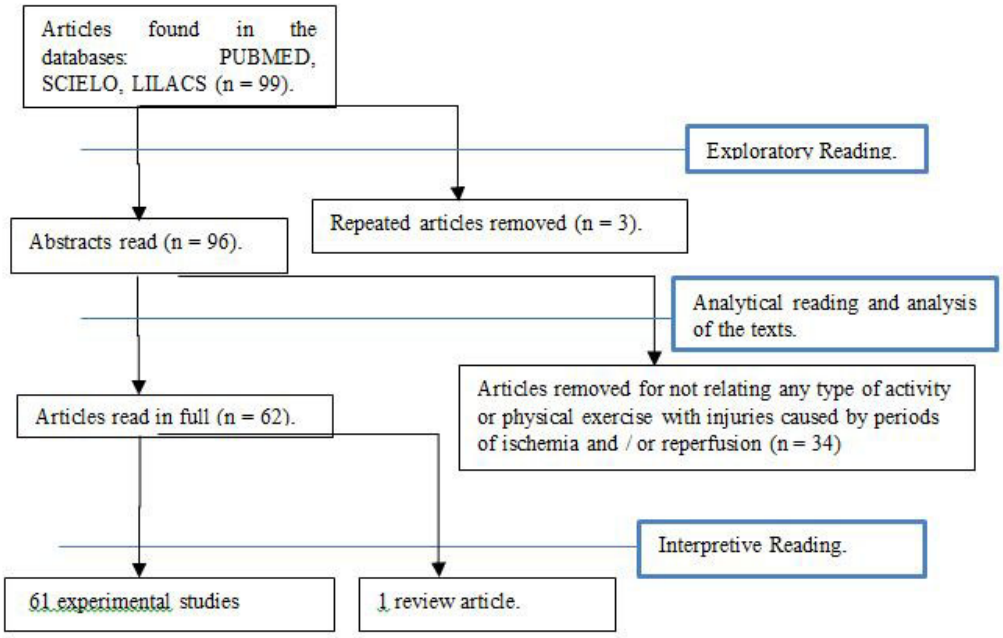

Figura 1 - Flowchart

RESULTS

99 articles were selected through the descriptors in the cited databases, of which only 62 were maintained based on the analysis of the inclusion and exclusion criteria, 3 articles were removed for being present in more than one database and 34 articles were removed after exploratory and selective reading because they did not relate any type of activity or physical exercise to injuries caused by periods of ischemia/reperfusion.

Table 1 below contains the articles that corresponded to all defined inclusion criteria, with their main author, year of publication and most relevant conclusion of each research, all of which are subsequently analyzed during the discussion in that study.

Table 1 – Articles

AUTOR	YEAR	CONCLUSION
Szabó et al. [10]	2018	Exercise increases MMP-2 activity and reduces fibrosis and minimizes ischemia-reperfusion injury in cardiac tissue.
Teixeira[11]	2017	Effects of hormonal treatments T3 and T4 were similar, or better, to those provided by aerobic physical training.
Alánová[12]	2017	Physical training does not amplify the cardioprotection afforded to hearts undergoing infarction due to continuous normobaric hypoxia.
Bulut[13]	2016	Estrogen receptor agonists, as well as oxytocin, in conjunction with exercise, may be new effective therapies to protect against myocardial ischemia in postmenopausal women.
Rinaldi[14]	2015	Data suggest that there is an early brain reaction to the induction of myocardial infarction, involving non-neuronal cells, which is attenuated by exercise.
Peng[15]	2017	Results revealed in first place that irisin mitigated neuronal damage induced by oxygen-glucose deprivation.
Shiragaki[16]	2019	Findings demonstrate that the electrical stimulus takes on common characteristics of exercise in the rat claudication model, which can facilitate investigations on the local mechanisms of exercise-induced functional recovery.
Sharma[17]	2019	The preconditioning of aerobic exercise significantly decreases the regulation of pathological events or biomarkers and increases the physiological biomarkers in the pre and post myocardial infarction phases.
Lu[18]	2018	Pre-conditioning relieves myocardial injury induced by exhaustive exercise through negative regulation of the cardiac KATP channels and autophagy.
Walters[19]	2015	The activity protects against long-term muscle damage, but not short-term neural injury or excitation-contraction decoupling.
Garza[20]	2019	Strength training can be beneficial for post-myocardial infarction by attenuating left ventricular dilation and concomitant cardiac dysfunction.
Xu[21]	2017	Moderate intensity physical training significantly increases the expression of TR-α1 and TR-β1 proteins, which in turn can increase α-MHC and improve myocardial contractile function and prognosis.
Schaun[22]	2017	Physical training partially preserved cardiac function and increased the intracellular antioxidant response in cardiac tissue after acute myocardial infarction.
Naderi[23]	2019	Physical training improved cardiac function and levels of stem cell and cardiomyocyte markers, and reduced the size of the infarction.
Cunha[24]	2017	Aerobic physical training improves plantar redox homeostasis in heart failure associated with a decrease in NADPH oxidase, activation of redox-sensitive proteins and proteasome hyperactivity, preventing atrophy.
Vujic[25]	2018	Cardiomyogenesis can be activated by exercise in the heart of normal and injured adult mice and suggests that stimulation of the generation of endogenous cardiomyocytes may contribute to the benefits of exercise.
Wang[26]	2018	Exercise grants certain aspects of its cardioprotective effects by activating the BDNF / TrkB axis in a NO-dependent manner.
Lee[27]	2017	Physical training can contribute to the improvement of muscle dysfunction and cardiac function after myocardial infarction.
Farah[28]	2017	Coronary endothelial cells, instead of cardiomyocytes, play a key role in exercise eNOS-dependent cardioprotection.
Glean[29]	2015	NO2− infusion can increase vascular control of skeletal muscle during exercise in rats with chronic heart failure.
Melo[30]	2019	Angiogenesis process may have influenced muscle recovery and reduced muscle atrophy of type I fibers in animals that exercised before cerebral ischemia.
Shen[31]	2015	Kinin B1 and B2 receptors play roles in exercise-induced cardiac muscle angiogenesis.
Pósa[32]	2015	Six weeks of voluntary exercise training preserved the heart from heart damage.
Schaun[33]	2017	Aerobic training before acute myocardial infarction partially preserves cardiac function.
Daliang[34]	2019	Aerobic exercise increased serum levels of netrin-1, myocardial netrin-1 and the DCC receptor and reduced the expression of myocardial MMP2 and MMP9 proteins, to improve the level of fibrosis after myocardial infarction in rats.
Calegari[35]	2018	Physical training attenuates the level of TNF-α and also improves the level of cytokine IL-10 in the skeletal muscle of rats with heart failure.
Sharma[36]	2018	Treatment with CuNP and physical training isolated or in combination favorably phosphorylates the GSK-3β kinase pathways and further decreases oxidative stress, inflammatory cytokines, apoptosis and increases the serum bioavailability of NO in ischemia-reperfusion injury in rats, which protects the damage myocardial.
Meng[37]	2017	Short- and long-term preconditioning can reduce myocardial injury after exhaustive exercise.
Sun[38]	2018	Exercise preconditioning plays its cardioprotective role by activating the JAK2 / STAT3 signaling pathway, reducing myocardial cell apoptosis and relieving myocardial ischemia injury.
Jia[39]	2018	Interval exercise increased the functional performance of the heart and was accompanied by reversal of pathological cardiac remodeling.
Bo[40]	2019	Interval training can improve the calcium transient and contractile function of the single ventricular myocyte in adult rats with myocardial infarction.

Table 1 – Articles

AUTOR	YEAR	CONCLUSION
Xiao[41]	2017	Controlled intermittent aerobic exercise can inhibit the TGFβ pathway through positive regulation for the expression of miR-29a and miR-101a and, ultimately, cause reduced fibrosis and scar formation in cardiac tissue.
Shi[42]	2017	MicroRNAs-17-3p contributes to exercise-induced cardiac growth and protects against adverse ventricular remodeling.
Lu[43]	2016	Type C natriuretic peptide and cardiac natriuretic peptide B receptor play an important role in preconditioning-mediated cardioprotection against high-intensity exercise-induced myocardial injury in rats.
Melo[44]	2015	Physical training restores the levels of microRNA-1 and −214 expression and prevents changes in NCX and Serca-2a protein and gene expression.
Xi[45]	2016	Follistatin-likel is a potential mediator of exercise-induced cardioprotection in rats after myocardial infarction.
Lu[46]	2015	High intensity interval training was superior to continuous training of moderate intensity regarding the attenuation of oxidative stress and the improvement of myocardial glycolipid metabolism after myocardial infarction.
Feriani[47]	2017	The combination of physical training and pyridostigmine bromide promote some additional benefits in cardiovascular autonomic modulation and in the inflammatory profile in infarcted rats.
Wang[48]	2018	Wheel running increased the kinetics of the cardiomyocyte cross-bridge, the sensitivity to Ca2 + and the responsiveness of the contractile function to the stimulation of the β-adrenergic receptor in both sexes studied.
Danes[49]	2018	Physical exercise generates a protective mechanism that limits the level of myocardial acidosis and subsequent damage that accompanies ischemia-reperfusion stress.
Li[50]	2019	The level of autophagy activated during the cardioprotective phase initiated by preconditioning may be partially involved in the cardioprotective effects.
Parry[51]	2017	Protein synthesis and protein degradation are linked to cardioprotection associated with exercise and mitochondrial susceptibility for the first time in ischemia-reperfusion in cardiac tissue.
Bozi[52]	2016	Study provides evidence for the attenuation of aerobic physical training of cardiac endoplasmic reticulum stress by restoring quality control of cardiac protein, which contributes to better cardiac function in rats with post-myocardial infarction heart failure.
Guizoni[53]	2016	Late exercise improves systolic function and modulates intracellular calcium signaling proteins in rats with moderate and large myocardial infarction.
Alleman[54]	2016	Exercise helps support post-ischemic mitochondrial bioenergetics and redox homeostasis.
Bei[55]	2017	The exercise-induced increase in circulating extracellular vesicles intensifies the protective effects of endogenous extracellular vesicles against cardiac ischemia-reperfusion injury.
Feng[56]	2018	Early aerobic exercise combined with hydrogen-rich saline water treatment has the potential to be a new preventive measure to protect myocardial injury after myocardial infarction.
Cai[57]	2018	All types of exercises can effectively inhibit skeletal muscle atrophy by increasing antioxidant capacity, reducing oxidative stress and protein degradation and regulating the expression of growth factors in skeletal muscle.
Ranjbar[58]	2016	Ten weeks of aerobic physical training and L-arginine supplementation promote the arteriogenesis of the cardiac and gastrocnemius muscles.
Togoe[59]	2019	High-intensity aerobic training in an animal model of kidney disease resulted in an increase in the number of muscle fibers with a smaller cross-sectional area.
Lavorato[60]	2016	The combination of early therapy with mesenchymal stem cells and resistance exercises does not enhance the benefits of such treatments for structural and functional cardiac remodeling in infarcted rats.
Huang[61]	2016	Physical training suppressed apoptotic pathways dependent on the cardiac Fas receptor induced by ovariectomy and dependent on mitochondria in ovariectomized rat models.
Chen[62]	2015	The proposed system provides greater neuroprotection in an animal stroke model compared to a conventional treadmill and a motorized wheel for a certain exercise intensity.
Confortim[63]	2019	Acrobatic exercise can be a good therapeutic option, especially in children affected by neonatal ischemic-hypoxia and can be responsible for good results in cognitive and motor aspects.
Zhou[64]	2018	Study provided a preliminary basis for future research on the therapeutic effect of voluntary movement training against stroke-induced neuronal damage.
Li[65]	2017	Irisine reduces neuronal injury induced by ischemia through activation of the Akt and ERK1 / 2 signaling pathways and contributes to the neuroprotective effect of physical exercise against cerebral ischemia.
Kiuchi[66]	2019	The role and relevance of new tools for the sympathetic nervous system was discussed.
Smenes[67]	2018	Exercise can make the myocardium and mitochondria more vulnerable to perioperative damage.
Yuan[68]	2018	Exhaustive exercise causes severe injuries to cardiomyofibrils, inducing hypoxia-ischemia and altering the ultrastructure.
Liao[69]	2015	Long-term high-intensity exercise training would induce cardiac hypertrophy accompanied by damage to the heart, leading to a risk of pathological changes.
Reyes[70]	2015	Exercise can be a secondary stressor in cardiac function.
Carfagna[71]	2015	G. sulphuraria's ability to reduce oxidative damage associated with exercise and mitochondrial dysfunction makes it potentially useful even in other conditions that lead to oxidative stress, including hyperthyroidism, chronic inflammation and ischemia-reperfusion.

DISCUSSION

There is a consensus in the scientific literature that physical exercise is beneficial to the human body, such as, for example, its cardioprotective effects[10-13], neuroprotective effects[13-15] and improved angiogenesis[16], however, by detailing each of these benefits and how it is caused, the knowledge is vast, but not complete.

In this sense, aerobic physical exercise increases strength and consolidates the cardiac muscles to work even stressed[17,18], protecting against muscle damage in the long term[19]. Results demonstrate that strength training can be beneficial for post myocardial infarction, attenuating left ventricular dilation and concomitant cardiac dysfunction associated with myocardial infarction[20], while resistance training increases the inner dimensions of the left ventricle as a result of expansion plasma concentration induced by albumin[20]. Moderate intensity physical training, in contrast, significantly increases the expression of the TR-α1 and TR-β1 proteins, which in turn can positively regulate the αmyosin heavy chain and improve myocardial contractile function and the prognosis after myocardial infarction[21].

Cardioprotective Effect and Anti-Oxidant Response

In addition, these studies demonstrate that physical training partially preserves cardiac function and increases the intracellular antioxidant response in the cardiac tissue of animals after acute myocardial infarction[22].

When performed at different intensities, physical training improves cardiac function and levels of stem cell and cardiomyocyte markers, reducing the size of the infarction. Furthermore, it has been reported that high intensity exercises cause greater increases than low and moderate intensity exercises[23], which shows that the intensity of exercise has a high influence on its effects. Aerobic physical exercise prevented the signs of heart failure and skeletal muscle atrophy in rats with trained myocardial infarction, which showed a better tolerance to exercise, attenuated cardiac dysfunction and increased the transverse area of the plantar fiber[24]. Aerobic physical activity improves redox homeostasis in heart failure associated with a decrease in NADPH oxidase, activation of redox-sensitive proteins and proteasome hyperactivity, further preventing the atrophy[24]. These data reinforce the role of aerobic exercise as an efficient therapy for loss of muscle mass in heart failure. Exercise after myocardial infarction also induces a robust cardiomyogenic response in an extended border zone of the infarcted area[25].

Neurotrophic Axis Activation and Angiogenesis

In an experimental study conducted with rats, it was observed that the rats in the exercise group exhibited increased myocardial angiogenesis and improved cardiac function[26].

Overall, the results demonstrate that exercise confers certain aspects of its cardioprotective effects through activation of the brain-derived neurotrophic factor/TrkB axis in a NO-dependent manner[26], a process in which fluid-induced shear stress can play a crucial role. The brain-derived neurotrophic factor is induced by physical training in skeletal muscle and in the non-infarcted area of the left ventricle27, which can contribute to the improvement of muscle dysfunction and cardiac function after myocardial infarction[27].

Beyond that, about NO, it was observed that it is the coronary endothelial cells, instead of cardiomyocytes, that play a fundamental role in eNOS-dependent cardioprotection[28]. In addition, data demonstrate that NO2- infusion can increase the vascular control of skeletal muscle during exercise in rats with chronic heart failure2[29]. In other studies, the extended process of angiogenesis was repeated[30,31], which shows the consistency of this information. The levels of mRNA and protein at the B1 and B2 receptors in the physical training group were significantly higher than those in the group with myocardial infarction, superior than those in the control group[31]. The capillary number in the heart muscle also showed the same trend.

There was a correlation between capillary number and B1 receptor protein (not B2 receptor protein) in all groups. Therefore, the Kinin B1 and B2 receptors play a role in exercise-induced cardiac muscle angiogenesis. However, the B1 receptor appears to have a more prominent role[31].

Signaling Paths Activated by Physical Exercise

In another study, after a six weeks training, preservation of the heart was obtained against cardiac injuries, which also associated this protection mechanism with the decrease in the activity of matrix-2 metalloproteinases[32].

Aerobic training associated with an acute myocardial infarction is also responsible for an increase in GLUT4[33] expression and increased serum levels of netrin-1, myocardial netrin-1 and DCC receptor, reduced the expression of myocardial proteins MMP2 and MMP9, to improving the degree of fibrosis after myocardial infarction in rats[34], and also not only attenuates the level of TNF-α, but also improves the level of cytokine IL-10 in the skeletal muscle of rats with heart failure[35].

Furthermore, treatment with CuNP and physical training, in isolation or in combination, were pointed out, because they favor the GSK-3β kinase phosphorylate pathways and further reduce oxidative stress, inflammatory cytokines, apoptosis and increase serum NO bioavailability in rats that have suffered with ischemia-perfusion, which tends to protect myocardial damage[36]. In addition, long-

term physical exercise significantly inhibits Caspase-8 expression, 3 mRNA and reduces protein synthesis[37].

Physical activity also plays a cardioprotective role, by activating the JAK2/STAT3 signaling pathway, reducing myocardial cell apoptosis and relieving myocardial ischemia damage[38]. Interval physical exercise increased the functional performance of the heart and was accompanied by the reversal of pathological cardiac remodeling and increased the expression of leukemia inhibitory factor and leukemia inhibitory factor receptor, activated signal transducer and transcription activator (STAT3)[39] and, it can also improve the transient and contractile calcium function of the single ventricular myocyte in adult rats with myocardial infarction[40].

Controlled intermittent aerobic exercise can inhibit the TGFβ pathway through the positive regulation of the expression of miR-29a and miR-101a and, finally, cause reduced fibrosis and scar formation in cardiac tissue[41].

While miR-17-3p contributes to exercise-induced cardiac growth and protects against adverse ventricular remodeling[42], it may represent a new therapeutic target to promote the functional recovery after cardiac ischemia-reperfusion.

The type C natriuretic peptide and the cardiac natriuretic peptide B receptor play an important role in cardioprotection mediated by exercise preconditioning against myocardial injury induced by high-intensity exercise in rats[43]. As well, it restores the levels of microRNA-1 and 214 expression and prevents changes in the expression of proteins and genes of NCX and Serca-2ª44. Exercise has been reported to improve functional performance, reduce fibrosis of hearts with myocardial infarction, and induce FSTL1 expression, TGFβ-Smad2 / 3 signaling and myocardial angiogenesis[45].

Aerobic physical exercise, especially high intensity type, significantly increases mRNA levels and maximum phosphofructokinase-1 and carnitine palmitoyl transferase-1 activity, as well as the maximum proportion of ATP46 synthesis. High-intensity training was superior to moderate-intensity training in its ability to improve cardiac function and exercise capacity in a post-MI46 rat model. High-intensity training was also superior to moderate-intensity training with regard to the attenuation of oxidative stress and the improvement of myocardial glycolipid metabolism after myocardial infarction[46].

Aerobic physical exercises, associated or not with the treatment of pyridostigmine bromide in animals with myocardial infarction, were capable of: reduction of the myocardial infarction area, systolic and diastolic function, baroreflex sensitivity, cardiovascular autonomic modulation and tonic activity of the sympathetic and parasympathetic nervous system[47].

Myoprotective Effect

Regular exercise significantly increased the speed of relaxation and shortening of ventricular myocytes and the rate of increase in intracellular Ca2 + transients and improved the response of biomechanics and Ca2 + reuptake to β-adrenergic stimulation[48]. Conclusions were also found about the increase in the capacity to deal with acidosis conferred by physical training, which improves tolerance and the results of exercise in response to myocardial ischemia and reperfusion injury[49]. Other results suggest that the level of autophagy activated during the cardioprotective phase initiated by preconditioning to exercise may be partially involved in the cardioprotective effects, maintaining a basal level of normal autophagy during the subsequent exhaustive exercise in the rat myocardium[50]. Findings also link protein synthesis and degradation (protein quality control mechanisms) with exercise-linked cardioprotection and mitochondrial susceptibility for the first time in cardiac ischemia and reperfusion[51].

Aerobic training attenuates oxidative stress, mitochondrial dysfunction and calcium imbalance[52], can be a potential strategy to restore cardiac homeostasis of the endoplasmic reticulum. Aerobic training attenuated the endoplasmic reticulum stress induced by myocardial infarction, reducing the protein levels of the unfolded protein response markers and the accumulation of folded and polycycliced proteins[52], which was associated with restored proteasome activity.

Physical Exercise in Post Ischemic Conditioning

Late exercise improves systolic function and modulates intracellular calcium signaling proteins in rats with moderate and large myocardial infarction[53]. Calsequestrin expression increased in the exercised groups compared to the sedentary ones[53]. Exercise helps to support post-ischemic mitochondrial bioenergetics and reduction-oxidation (redox) homeostasis, which is associated with the preserved mitochondrial membrane potential and protection against reperfusion arrhythmia[54]. The exercise-induced increase in circulating extracellular vesicles intensifies the protective effects of endogenous extracellular vesicles against ischemia and reperfusion cardiac injuries, thus, exercise-derived extracellular vesicles can serve as a potent therapy for myocardial injury in the future[55].

Early aerobic exercise combined with hydrogen-rich saline water increased the induced myocardial infarction levels of superoxide dismutase and the total antioxidant capacity, attenuated the induced myocardial infarction levels of malondialdehyde and catalase[56]. In another study, exercise negatively regulated mRNA levels of murf1 and atrogin-1, decreased the level of reactive oxygen species, increased antioxidant capacity, regulated the expression of insulin-like growth factor 1 (IGF1), mechanical growth (MGF), neuregulin1 (NRG1) and myostatin (MSTN), and activated Akt and Erk1 / 2 signaling in the soleus muscle[57].

It was found, in one experiment, that 10 weeks

of aerobic training and laryngine supplementation promote arteriogenesis of the cardiac and gastrocnemius muscles in parallel to the overexpression of TGF-β and negative regulation of angiostatin in rats with myocardial infarction[58]. Other results indicate that aerobic training protects the kidneys in ischemia and reperfusion injuries, and does not reverse the atrophy of muscle fibers with a greater transverse area, but increased the number of fibers with a smaller tanversal area[59].

The combination of early therapy with mesenchymal stem cells and resistance exercises does not enhance the benefits of such treatments for structural and functional cardiac remodeling in infarcted rats[60]. However, physical exercise suppressed the apoptotic cardiac pathways induced by ovariectomy and dependent on the Fas receptor and dependent on mitochondria in models of ovariectomized rats. These findings may indicate a new therapeutic effect for physical training to prevent cardiac apoptosis in women in menopause or bilateral oophorectomy[61].

Neuroprotective Effect

Experimental data demonstrated that a proposed focused system offers greater neuroprotection in a stroke model compared to a conventional treadmill and a motorized steering wheel for a certain exercise activity[62]. This proves that the effects of physical exercise on ischemic injuries vary according to the quantity and quality proposed. In another study, rats exercised ischemic performance and motor coordination better than sedentary ischemic rats (neuroprotective effect)[30].

Results show that acrobatic training can reverse hyperactivity and anxiety, also improves locomotion and reduces cerebral atrophy in animals with hypoxic-ischemic encephalopathy[63]. This can be adapted to treat children with this encephalopathy in the future. In another study, prolonged exercise normalized these morphological changes in microglia and astrocytes in the prefrontal cortex, hippocampus and thalamus, but not in PVN. Our data suggest that there is an early brain reaction to the induction of myocardial infarction, involving non-neuronal cells, attenuated by prolonged exercise[14].

In a survey, it was possible to observe that movement training based on will, search for food, for example, exhibited an improvement in neurobehavioral performance in comparison to other types of training[64].

A recent study found that irisin, a myocin derived from skeletal muscle recently discovered during exercise, is also synthesized in various tissues of different species and protects against neuronal injuries in cerebral ischemia[15]. Irisin reduces ischemia-induced neuronal damage by activating the Akt and ERK1 / 2 signaling pathways and contributes to the neuroprotective effect of physical exercise against cerebral ischemia, suggesting that irisin may be a factor that links metabolism and cardiocerebrovascular diseases[65].

Possible Adverse Effects

In dogs, sympathetic stimulation of the renal nerves for 3 hours increased the neuronal activity of the left stellate ganglion, facilitating the occurrence of ventricular arrhythmias in the course of acute myocardial ischemia[66]. Other risk was reported in a different study in which the results indicate that exercise did not precondition the heart against damage related to surgery[67]. Exercise can make the myocardium and mitochondria more vulnerable to perioperative damage. In addition, exhaustive exercise causes severe injuries to the cardiomyofibrils, inducing hypoxia-ischemia and altering the ultrastructure[68].

The results indicate that long-term training with high-intensity exercises would induce cardiac hypertrophy accompanied by damage to the heart, implying a risk of pathological changes. There may be an essential regulatory role for the mTOR signaling pathway in cardiac hypertrophy after moderate long-term exercise, but not after high-intensity exercise[69].

In another experimental study on male offspring with intrauterine growth restriction, exercise can be a secondary stressor of cardiac function. A reduction in cardiac performance was observed along with an increase in superoxide production in response to exercise in this susceptible group[70]. In addition, the ability of G. sulphuraria to reduce oxidative damage associated with exercise was discovered, and mitochondrial dysfunction makes it potentially useful even in other conditions that lead to oxidative stress, including hyperthyroidism, chronic inflammation and ischemia and reperfusion[71].

CONCLUSION

It can be concluded that there are several effects caused by physical exercise in ischemic injuries in the most diverse parts of the human body, with emphasis on the cardioprotective effect and the neuroprotective effect, in the literature it was possible to observe a considerable number of researches that sought to establish a protocol recommended in the amount of physical activity that would cause the best possible effect.

In addition, the knowledge about the mechanism of action for both beneficial and harmful effects to occur is not entirely clear, although a large number of signaling pathways are already known, it is still not possible to point exactly how the interaction occurs, with the thousands of molecules in the body, which generates variable results.

Finally, the high number of research aimed at creating new therapeutic or preventive measures using physical exercise isolated or as a complement to other medication shows the importance of this practice for maintaining the health of the human body.

Authors' contribution: Costa FC: writing of the scientific article, design and interpretation of results. Silva AFT: writing and reviewing the scientific article. Macedo BFS: writing and reviewing the scientific article. Silva GVN: writing and reviewing the scientific article. Silva TMMF: writing and reviewing the scientific article. Brito MVH: advise and review of the scientific article.

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