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Ischemic Preconditioning in Cardiac and Skeletal Muscle Induced by Exercise

Raúl Sampieri-Cabrera, Gustavo López-Toledo, Juan Manuel Aceves-Hernández and Virginia Inclán-Rubio

Abstract

Since it was discovered, ischemic preconditioning (IPC) has motivated research groups around the world to develop preconditioning protocols capable of protecting tissues against prolonged insults. In 31 years of study, promising results have been obtained on the beneficial role of the CPI and the mechanisms involved in its regulation. Also, different preconditioning protocols that have obtained results similar to the classic CPI have been developed, among which is the exercise-induced preconditioning (EP), that has been proven to protect the heart against an insult, mitigate the atrophy of the heart muscle and increase physical performance in athletes and/or athletes.

Keywords: cardiac, skeletal muscle, exercise-induced preconditioning, ischemic preconditioning, physical performance

1. Introduction

In 1986, Reimer studied the contribution of ATP depletion in the genesis of myocardial damage in an experimental model that involved the production of a series of brief ischemic episodes, assuming that successive ischemia decreased ATP levels. Conversely, Reimer was found to initially decrease the ATP content during the first ischemic episode, but the remaining episodes did not imply significant variation in ATP levels and, in some animals, these periods of ischemia produced cardioprotection [1]. This finding, which challenged the concept of successive episodes of ischemia, produces infarction as a result of “cumulative damage” [2].

Murry postulated that the maintenance of ATP in Raimer’s experiments, it could be because the myocyte needed less energy, as a consequence of the development of rapid adaptation to ischemia. To test this hypothesis, he performed a series of 4 periods of 5 minutes of ischemia and 5 minutes of reperfusion before the myocardium was submitted to a prolonged 40-minute ischemia. These brief periods of ischemia and reperfusion protect against ischemic damage and reduce 30% of the infarct size; He called this preconditioning or ischemic preconditioning (IPC) [3].

This finding contributed to the development of research lines to study the mechanisms involved in cardiac preconditioning, extending the concept of ischemic preconditioning in studies of: Arrhythmias [4], apoptosis [5] and endothelial dysfunction [6].

In addition, other non-ischemic stimuli have been studied to protect the heart, such as hypoxia [7], cell stretching [8], accelerated cardiac pacemaking [8] and physical exercise.

Exercise has been used as therapy for the treatment of stable ischemic vascular syndrome, where it has been observed that it improves perfusion in ischemic tissues. Some mechanisms involved in improving the perfusion of ischemic tissues after exercise involve:

- a. shear stress-associated improvement of endothelial function [9];
- b. increase in phosphorylation and expression of endothelial nitric oxide synthase [9];
- c. decrease in vascular oxidative stress; and
- d. collateral formation of vascular tissue.

Something that has to be clear when we talk about ischemic preconditioning is its dependence on the intensity of the stimulus (ischemia) and its duration, under this principle we can establish adequate protocols for the treatment of cardiovascular and muscular diseases; as well as, to improve the physical performance of the athletes.

Physical exercise challenges the organism to maintain stable conditions of the internal environment (homeostasis), against hypoxic conditions, oxidative stress and tissue nutrient deficiency. It is a condition of physiological stress, to be carried out continuously and through appropriate physical training programs provides benefits in the body, ranging from better control of blood glucose levels to better long-term memory.

There are multiple studies of the benefit of exercise in health, in all the virtues of exercise are praised. The result is obvious, improves and maintains the physical fitness, health and wellness of the person who performs it.

It has direct effects on muscle strengthening and cardiovascular capacity, in addition to the systemic effects involved with the release of substances into the bloodstream or the tissue that contribute to the preconditioning of the heart and skeletal muscle can be attributed to exercise.

The biochemical and physiological advantages conferred by exercise-induced preconditioning can serve to improve exercise performance. Although not all studies achieve this result, it is important not to forget that the participation of mediators produced and released during physical exercise and that are responsible for the beneficial effects in the body.

This chapter focuses on discussing the physiological mechanisms that are produced following an exercise-induced preconditioning protocol, especially those that relate to the cardiovascular system, skeletal muscle and physical performance.

2. Research methodology

An information search was carried out using the phrase “Preconditioning by exercise,” in the searcher of the database SN SciGraph Data Explorer 2019 of the springernature publishing house, finding 4, 953, 141 results, distributed in: ScholarlyArticle (3226063); Chapter (1264653); MonetaryGrant (300521); Patent (137092); MedicalStudy (19868); Book (1650); Periodical (1290); Concept (843); Subject (825); Address (99); Person (76); rdf: Property (61); rdfs: Class (38); Organization (22); Organization (10); Nonprofit (5); Facility (4);

ConceptScheme (4); Company (3); Other (3); BoardingPolicyType (2); Resource (2); EventStatusType (1); GamePlayMode (1); Archive (1); Education (1); Government (1); Healthcare (1); Ontology (1). Among these results, special interest was placed on using those that were 1 year old to date (with the exception of the classic articles that are related to clinical trials). A second filter was made, selecting only those works that were directly related to cardiac tissue, skeletal muscle and physical performance. Focusing on the representative works of the area without ruling out negative or contradictory results.

3. Mechanisms of exercise-induced preconditioning (EP)

3.1 About the cardiovascular system

The different cardiac affections, including myocardial infarction and ischemic heart diseases, are the main trigger of a high worldwide mortality, which originates in the sedentary lifestyle, chronic hyperglycemia and atherosclerosis. Although vigorous exercise itself induces a temporary hypoxia that causes damage to the myocardium, EP regulates down-pathological biomarkers and increases physiological biomarkers in both the pre-and post-myocardial infarction phase [10].

The protective effects of physical exercise on the cardiovascular system are carried out on cerebral blood flow, vascular endothelium, vascular vasodilation, endothelial progenitor cells, collateral circulation and cardiac muscle.

Despite the traditional knowledge of the benefits of aerobic exercise in health, it has not yet been introduced in the clinical setting. Knowing the benefits of exercise in cardiovascular and cerebrovascular diseases can encourage more patients with cerebral infarction and myocardial infarction and people with high-risk factors, to accept exercise interventions for prevention and treatment, and to health professionals to include exercise therapies as adjuvants in pharmacological treatment and even as independent therapies [11].

It is believed that early aerobic exercise has the potential to be a precautionary strategy for myocardial injury after myocardial infarction, through the regulation of the expression of proteins related to antioxidants and proteins associated with mitochondria [12].

In the heart one of the main harmful events produced by an insult is myocardial injury. Where, the protective role of EP has been reported, through the down regulation of KATP channels and the reduction of autophagy [13].

A mechanism of classic myocardial injury is damage by reperfusion, where, it has been reported that EP decreases oxidative stress, inflammatory cytokines and apoptosis, and increases the serum bioavailability of NO. These mechanisms are regulated by the GSK-3 β pathway [14].

Interestingly, KATP channel opener drugs have been linked to cardioprotective events, where an increase in reactive oxygen species (ROS) has been reported, which downregulates the activity and expression of calcium channels in the tissue. Cardiac, which can mitigate the evolution of reperfusion damage. The positive regulation of ROS is related to the uncoupling of the respiratory chain, mainly in cardiomyocytes. Exercise, being a systemic event, activates complex mechanisms responsible for regulating body physiology, such as the vascular release of NO, which contributes to keeping the mechanical power of the heart regulated. On the other hand, as we know, an exacerbated increase in ROS, can generate tissue damage through mechanisms of cellular autophagy, so it is likely that time is a regulatory factor and of great importance in EP protocols. It is very difficult to perform an isolated study of the physiological role of EP, physiology seen as a complex

system challenges us to explain the phenomena from an integrative perspective that analyzes the phenomenon and its interactions with negative and positive regulation mechanisms.

From the therapeutic point of view the possible implications of PE, can contribute to improve the treatment of cardiovascular diseases, it has been reported that in a training protocol with vibration, increases cardiac tolerance to reperfusion injury after ischemia, decreases the size of the infarction and cardiac arrhythmias and facilitates spontaneous defibrillation [15]. These data suggest that exercise helps to regulate the participation of the electrical conduction system after a cardiac insult, the mechanisms by which this happens has not yet been elucidated.

It is known that the early response to a moderate and/or exacerbated cardiac insult eventually results in the generation of cardiac hypertrophy (increase in the volume of cardiomyocytes), which if not compensated, can progress to heart failure. Exercise has been related to a type of beneficial hypertrophy known as physiological hypertrophy, in which, far from having repercussions that compromise cardiac capacity, they improve it. On the other hand, there is pathological hypertrophy, which is linked to the development of myocardial scar and low cardiac capacity.

Treatments for cardiac hypertrophy are related to stopping the causal stimulus, which prevents its progression. In this sense, recently, PE has been reported to attenuate pathological cardiac hypertrophy by increasing the functional capacity of the cardiovascular system, through the MAPK pathway [16]. Probably this protective effect is related to the systemic increase of ROS, one of the main stimuli that regulate the MAPK pathway.

On the other hand, the level of autophagy activated during EP may be partially involved in the cardioprotective effects, maintaining a basal level of normal autophagy in the myocardium during the subsequent exhaustive exercise [17]. This ability of the EP to activate autophagy processes helps to sense the cellular metabolic processes, thus maintaining the homeostasis of cardiomyocytes.

Although in general, it is believed that preconditioning is directly triggered by a brief ischemia-reperfusion. It is known that brief ischemia produces transient dilatation (or stretching) of the heart. Therefore, it has been postulated that the stretching of the myocardium may be responsible for preconditioning, through the ion channels activated by stretching [18]. This idea can be supported indirectly by the fact that in chronic exercise, by increasing endothelial shear stress, increases NO production and ECNOS gene expression and can contribute to the beneficial effects of exercise in the cardiovascular system (ie say, antihypertensive) [19]. Although, as mentioned above, to say that the protective effect of preconditioning is due to a particular mechanism and not to a complex process, it is risky and simplistic.

The beneficial role of exercise on the cardiovascular system inevitably involves the regulation of vasodilation and vasoconstriction. In this sense, in stable coronary artery disease (CAD), exercise has been used as a treatment due to its endothelium-dependent vasodilator capacity, induced by acetylcholine. The molecular mechanism involved is through the phosphorylation of the eNOS-induced for Akt pathway [9]. This study demonstrates the role of exercise as a therapy in cardiovascular diseases, its actual use in therapy and the mechanism of action involved. To the extent that EP protocols are standardized and establish molecular relationships between the preconditioning processes, progress may be made in the non-pharmacological and/or combined treatment (drugs and exercise) of cardiovascular diseases.

Not only has it been linked to EP for the treatment of cardiovascular diseases, but it has also been shown to be useful for the treatment of doxorubicin poisoning (DOX), where it has been described that 2 weeks of EP are sufficient to prevent cardiorespiratory dysfunction associated with DOX and prevent mitochondrial

dysfunction by reducing mitochondrial DOX accumulation [20]. The role of PE in poisoning processes can focus the bases to study its implications in pharmacokinetics and thus establish therapies with better efficiency and fewer adverse reactions and/or drug interactions.

In addition, in a novel way, it has been described that PE induces a pro-angiogenic medium that can increase the therapeutic effects of stem cells derived from adipose tissue in cardiac remodeling after myocardial infarction [21], so its potential in genetic medicine, it is promising and can contribute to generating favorable tissue environments for cell insertion and even in organ transplants.

Recently, it has been described that training with 12-week exercises in patients with heart failure mitigates ischemic injury due to endothelial reperfusion, protection mechanisms can be linked to PE [22]. This result is the first of its kind in a disease as complex as heart failure, so in a few years it is highly probable that within the treatment schemes for cardiovascular diseases exercise protocols are recommended. The challenge for health professionals is still great. Multidisciplinary groups must be established to develop and execute the protocols, monitor patients, evaluate therapies and make adjustments to obtain the expected results.

3.2 About skeletal muscle

Skeletal muscle represents one of the most abundant tissues of the organism, for many years its mechanical and structural role has been studied, without studying its role in the regulation and maintenance of energy metabolism, release of humoral factors, regulation of oxidative stress, among others. Physical exercise represents the participation of the cardiovascular, respiratory and naturally skeletal muscle systems. For this reason, it is not to be expected that the protective role of the EP will positively impact the skeletal tissue. The mechanisms involved in the production of the beneficial effects of preconditioning in skeletal muscle are not yet clear, although it has recently been shown to decrease skeletal muscle atrophy induced by the discharge of the hind limbs (HU) and the mechanism that can participate it is through HDAC4/Gadd45 α [23]. Although, interestingly, the mechanisms of physical training to reduce muscle atrophy are associated with the biogenesis, function and redox balance of mitochondria, the same mechanism involved in preconditioning [24]. The redox mechanism seems to be common in preconditioning processes regardless of white tissue, probably not the only shared mechanism, but certainly unlike the cardiac muscle, in skeletal muscle hypertrophy represents a greater capacity for energy regulation.

On the other hand, the mechanisms involved in changes in the markers of muscle damage and the parameters associated with running economy (ER) are not related, that is, increasing the tissue damage in skeletal muscle does not improve the ER [25]. However, it is likely that in order to represent an improvement in the ER, a chronic protocol must be performed.

EP decreases arterial circulation in skeletal muscle, this confers hypoxia in the tissue. It has been reported that hypoxic preconditioning (HPC) can protect the function of respiratory skeletal muscle during reoxygenation through signaling cascades sensitive to redox mechanisms and the regulation of mitochondrial channels [26].

The protective effect of EP on skeletal muscle can be used for the treatment of muscular atrophy and strengthening of muscle tissue. It is still necessary to study the mechanisms that can contribute to improve it and optimize the protocols that are adapted to the physiological needs of patients.

On the other hand, preconditioning reduces the fatigue associated with repeated exercise speed [27], however, it is still necessary to establish exercise protocols

where the variables to be studied are identified and correlated with an increase in physical performance and/or increase of the ER.

3.3 About physical performance

The role of EP in physical performance is controversial, while some papers report that EP improves physical performance, others have not found changes with respect to control groups. In part, this is because EP protocols are not optimized.

Studies using remote IPC improve the performance of the swimming, cycling and running time test in a range of ~3–5%. However, in other studies, the CPI seems to have no effect on physical performance.

Although what most studies want to demonstrate is the increase in performance by the IPC, it is difficult to obtain promising results if the participation of the biochemical mediators produced during the IPC is overlooked and who are responsible for the beneficial effects of the exercise in the organisms, regardless of whether they confer improvements in physical performance or not. Until now, the mechanisms that contribute to the possible benefits of the IPC in physical performance are not fully defined, but they can be the same as those activated during the classic IPC. It has been described that the IPC improves the performance of supramaximal exercise by increasing accumulated oxygen deficit (AOD), an indicator of glycolytic capacity, so that a greater glycolytic capacity due to the increase in AOD could be a potential mediator involved in improving physical performance [28].

It has been reported that improved metabolic stress increases ischemic preconditioning for exercise performance, amplification of the ischemic preconditioning stimulus increases the effect on exercise capacity [29].

In addition, in the aerobic function and the performance of the 4 km cycling time test, it suggests that the acute CPI shows some potential as a strategy to improve performance for well-trained cyclists before high-intensity exercise [30].

On the other hand, coupled with the molecular mechanisms associated with the beneficial effect of EP in the cardiovascular system, the nervous system through vagal cardiac control in high-strength athletes has generally been associated with adequate recovery to training and preparation to face the high-intensity training. Therefore, a method that improves vagal cardiac control in endurance athletes could be advantageous. IPC increases rapid cardiac vagal reactivation after exercise at exercise intensities below the lactate threshold in endurance runners [31].

However, some negative reports about preconditioning on physical performance indicate that remote ischemic preconditioning (RIPC) does not have a practical ergogenic impact on speed skating performance on long runs of 1000 m in elite athletes. The relevance of using RIPC during training to increase physiological stress in sprinters deserves further investigation [32].

The IPC does not improve sprint performance of 10 or 20 m in athletes [33]. Although the IPC accelerated recovery to a certain extent in the short term, the long-term recovery of the autonomous cardiac control of the repeated sprint exercise (RSE) did not change, and this accelerating effect was not accompanied by any effect of the IPC on surrogates of the responses of energy metabolism to RSE [33].

It is extremely important to standardize EP tests in order to establish adequate exercise plans to increase physical performance in athletes and improve their health conditions.

The role of EP to improve physical performance of athletes seems to be a field with many controversies, this is due to the great variability between the protocols used, the type of exercise to which the athletes are subjected, the variables studied, to name a few.

The EP confers protection to the tissues, perhaps immediately this does not translate to improve physical performance, but in a prolonged time course is likely to indirectly contribute to increase it.

4. Conclusion

This chapter describes the mechanisms involved in the protective effect of EP on the cardiovascular system, skeletal muscle and physical performance. Although EP seems to contribute to mitigate tissue damage due to ischemia, the role of calcium in PD, the molecular interactions it evokes, the contribution of pH, the role of blood volume and temperature, among others, are still to be understood.

The EP studies are constantly increasing, we can find a lot of information in the scientific literature, in much of this information we discuss the protective role of PD on tissues (even in the nervous), but there is other information that is little clear and seems to encourage discussion between different research groups, this one speaks on the one hand of the possible role of EP in improving physical performance and on the other hand, those who document not finding improvements in physical performance after a EP protocol.

In this sense, it is important to clarify that preconditioning is a multifactorial phenomenon, and that its success depends to a large extent on the protocol used and the rigorous control of the variables, in addition it is a phenomenon highly dependent on the type, ie there are windows temporary in which we can observe preconditioning and others where we have damage. In addition, preconditioning is a reversible phenomenon, that is, its protective role can only be observed in periods of time, although there has been talk of a muscle memory, it seems to exist only if the ability to challenge the body to activate it is preserved. Sequential.

EP is undoubtedly one of the most interesting phenomena of exercise physiology, its therapeutic potential is real, it is being used in the clinic, it is used in the exercise protocols, but if we want to understand the phenomenon we must work seriously to elucidate the mechanisms that participate and how they relate to each other, that is, to study the complexity of the system with the greatest control of the variables and under standardized protocols.

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Conflict of interest

The authors declare no conflict of interest.

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