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Mechanisms Involved in Cardioprotection Induced by Physical Exercise

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Abstract

Significance: Regular exercise training can reduce myocardial damage caused by acute ischemia/reperfusion (I/R). Exercise can reproduce the phenomenon of ischemic preconditioning, due to the capacity of brief periods of ischemia to reduce myocardial damage caused by acute I/R. In addition, exercise may also activate the multiple kinase cascade responsible for cardioprotection even in the absence of ischemia. **Recent Advances:** Animal and human studies highlighted the fact that, besides to reduce risk factors related to cardiovascular disease, the beneficial effects of exercise are also due to its ability to induce conditioning of the heart. Exercise behaves as a physiological stress that triggers beneficial adaptive cellular responses, inducing a protective phenotype in the heart. The factors contributing to the exercise-induced heart preconditioning include stimulation of the anti-radical defense system and nitric oxide production, opioids, myokines, and adenosine-5' triphosphate (ATP) dependent potassium channels. They appear to be also involved in the protective effect exerted by exercise against cardiotoxicity related to chemotherapy. **Critical Issues and Future Directions:** Although several experimental evidences on the protective effect of exercise have been obtained, the mechanisms underlying this phenomenon have not yet been fully clarified. Further studies are warranted to define precise exercise prescriptions in patients at risk of myocardial infarction or undergoing chemotherapy.

Antioxid. Redox Signal. 00, 000–000.

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The concept that regular physical activity is beneficial for the cardiovascular apparatus is a cornerstone in the history of Medicine. A great bulk of data has been produced demonstrating that exercise decreases the incidence and the prevalence of myocardial infarction and augments the chances of survival after a cardiac event (1, 112, 156, 157). However, the beneficial effects afforded

by regular exercise cannot be explained by only taking into consideration the improvement in classical cardiovascular risks, such as reduction in blood pressure, improved glucose homeostasis, and low cholesterol and blood triglycerides. It was estimated that these risk factors explain only 27–41% of the global cardioprotection conferred by active lifestyle. It is then probable that other still elusive factors related to exercise exert protective effects on the cardiovascular system (176). Thus, mechanisms of cardioprotection are still to be fully elucidated. One phenomenon that may at least in part explain why exercise is cardioprotective is ischemic preconditioning (IP), which refers to the possibility that brief sub-lethal ischemic insults render the heart more resistant to subsequent more profound ischemia, causing infarction. Moreover, IP can also protect from damage due to reperfusion and to the progression of coronary patients toward heart failure. It appears that exercise can mimic the effect of IP, thereby explaining some of its beneficial effects. Actually, it appears that exercise can initiate the biochemical cascade of IP without the need of ischemia. Specifically, exercise induces the accumulation of several metabolites (adenosine, bradykinin, opioids, and possibly others), which are normally produced during effort and that trigger preconditioning. Exercise can also increase the production of nitric oxide (NO), reactive oxygen species (ROS), and heat shock proteins (HSPs). All these substances are believed to be involved in the classic form of IP. Moreover, exercise can mimic the phenomenon of remote preconditioning, which refers to the possibility to precondition the myocardium by inducing ischemia in a remote organ or tissue. Finally, exercise has been found to be able to protect against cardiotoxicity due to antineoplastic drugs (21, 161, 172, 182). In the present review, we will summarize findings supporting the concept that regular exercise is cardioprotective against several insults and the related putative mechanisms.

Reperfusion Injury and Cardiac Conditioning

In western countries, the main causes of death and morbidity are acute coronary and heart diseases. Numerous researches have been performed in the study of acute coronary syndromes without ST elevation, the more frequent from the clinical point of view. The prognosis of these patients has been improved through both antithrombotic treatment and invasive strategies, such as primary angioplasty, which allows the direct restoration of perfusion (194, 195). However, it has been reported that reperfusion may cause additional damage to previously ischemic tissues. The immediate restoration of the blood flow is followed by a cascade of events that are able to trigger a vicious circle, characterized by inflammatory responses and more widespread local lesions, which determine the extension of the infarct size in otherwise vital tissues. This finding led to the concept of myocardial reperfusion injury (124, 195). Ischemia/reperfusion (I/R) damage is caused by complex mechanisms that include mechanical, extracellular, and intracellular processes (129, 195). A short description of the principal mechanisms involved in reperfusion injury is reported in Figure 1. They include: (i)

Ca²⁺ overload; (ii) ROS generation; (iii) lower production of NO; (iv) opening of the mitochondrial permeability transient pore (mPTP); (v) activation of bAU4 NFκB and other transcription factors; and (vi) no-reflow phenomenon. (i) The Ca²⁺ overload developed during ischemia is subsequently increased during reperfusion. After ischemia, the increased amount of Ca²⁺ at the cytosolic level results in structural fragility, whereas during the reperfusion phase the Ca²⁺ overload is responsible for a progressive increase in ventricular diastolic pressure (contracture) and necrosis of the contractile apparatus (149, 167). The Ca²⁺ overload favors the expression of proapoptotic elements from mitochondria and an increase in cellular osmolarity with consequent swelling (explosive swelling) of myocytes (198). Moreover, the Ca²⁺ overload is also responsible for mPTP opening (141). (ii) ROS generation: The main culprit of both the large release of cardiac enzymes and cell death occurring during reperfusion is the massive production of ROS. According to Hearse et al., the term “oxygen paradox” was conceived to explain the effects of ROS on the heart (7, 78). Both an increased production of superoxide anion (O₂⁻) and the activation of various enzymatic complexes have been observed after reperfusion and the reintroduction of oxygen. The presence of O₂⁻ and other ROS can considerably oxidize the cardiomyocytes already damaged by ischemia, thus favoring cell death (137, 181). During reperfusion, O₂⁻ reacts with NO, forming peroxynitrite (ONOO⁻). In addition, O₂⁻ can quench NO, thus reducing its bioavailability even in the absence of alterations of nitric oxide synthase (NOS) expression/activity (130). Consequently, the lower availability of NO can be attributed to the production of ONOO⁻, which, once produced, participates in myocardial damage, being highly cytotoxic at elevated concentrations (65, 127, 137, 158, 177). The production of ONOO⁻ not only contributes to both myocardial and vascular dysfunction during I/R but is also involved in other cardiac pathologies, such as myocarditis and chronic heart failure (50, 65, 127, 177). Importantly, ONOO⁻ cytotoxicity is reduced by the addition of NO through a secondary reaction (nitrosation reaction) (65, 137). The damage caused by O₂⁻ is reduced when this reactive species is transformed by the superoxide dismutase (SOD) into hydrogen peroxide (H₂O₂) (65, 127). In addition, the presence of Fe²⁺ or Cu²⁺ is able to transform H₂O₂ into hydroxyl (OH[•]) and hydroxyl (HO⁻) radicals, which are decidedly more toxic than O₂⁻ and H₂O₂, with consequent decreased toxicity. The release of ROS by mitochondria is dependent on mitochondrial depolarization, the opening of mPTP, and the ROS themselves, a phenomenon known as “ROS-induced ROS release.” This phenomenon induces a consequent large burst of ROS from mitochondria (65, 200). In the past decade, accumulating evidence suggested that the mitochondrial flavoenzyme monoamine oxidase represents another major source of ROS in the I/R myocardium (28). Probably, a reduced formation of H₂O₂ during reperfusion proves to be protective, provided that it is adequately formed or added, to reduce ONOO⁻ cytotoxicity and, consequently, the opening of mPTP. (iii) Reduced availability of

NO: NO is produced by vascular endothelial cells to prevent the reduction of antioxidants, thereby limiting oxidative stress injuries. After I/R, the presence of NO has a dual task: At high concentrations, it diminishes the harmful effects exerted by the endothelin and on the other hand improves microcirculation. During ischemia, NOS is transformed into “uncoupling NOS” capable of producing ROS, thus aggravating I/R damage. In this condition, ROS produced by the NADPH oxidase system, the mitochondrial electron transport chain, the decoupled NOS system, and the xanthine oxidase system can accumulate within the cells and reduce the effects of an antioxidant agent (189). (iv) mPTP opening: mPTP is a nonspecific pore placed in the inner mitochondrial membrane, whose opening at the beginning of reperfusion causes cell death (9, 32, 58, 63, 66, 74, 103). Among the main mechanisms responsible for mPTP opening during reperfusion, Ca²⁺ overload has received particular attention. During ischemia, the mitochondrial overload of Ca²⁺ would bring the mitochondria to the threshold at which the opening of mPTP occurs, and during reperfusion the true opening of the pore would be encountered. This phenomenon has been described as “mitochondrial trigger” (186). Although during ischemia the opening of mPTP is unlikely, since it is strongly inhibited by acidosis, it is instead favored during reperfusion, a phase in which exhaustion of adenosine-5'-triphosphate (ATP), oxidative stress, and high intramitochondrial concentrations of Ca²⁺ occur (74, 103). Therefore, the ideal scenario for the opening of mPTP is associated with the phase of reperfusion, in which on the one hand there is a massive increase of ROS and [Ca²⁺], and on the other the recovery of physiological pH within the cell (58, 74). (v) Activation of NFκB: NFκB is a dimer consisting of p50 and p65 subunits that are sensitive to the redox state and capable of determining rapid response to oxidative stress, constituting an important transcription factor involved in I/R damage. The active form of NFκB is transferred to the nucleus, where it activates target genes for transcription. In particular, NFκB is able to regulate the genes of numerous molecules, including NOS, cytokines (tumor necrosis factor α, interleukin [IL]-1), chemokines (ENA78), and ICAM-1. Its involvement in I/R damage has been suggested by the protective effect exerted by the administration of NFκB inhibitors in animal models (189). (vi) In addition, it should be remembered that the reduced availability of NO results in vasoconstriction and microthrombus formation in the lumen of small vessels(137),which, combined with the adhesion of leukocytes to the endothelium, lead to the so-called “no-reflow phenomenon” (5).

Protective Pathways and Mechanisms involved in Ischemic Pre- and Postconditioning

Short intermittent periods of I/R exert protective effects, both when applied just before infarct ischemia (IP) and immediately at the beginning of reperfusion (ischemic postconditioning [PostC]) (bF2 Fig. 2). The main transduction paths related to the conditioning mechanisms will be briefly described later and are shown in Figure3. SeealsoRefs.(27,68, 70, 79, 129). Despite the different

timing, both IP and PostC use the same innate cardioprotective mechanisms, both involving receptors and kinases coupled to G proteins and having mPTP as end-effectors. However, there are some differences between the molecular pathways involved. In the case of IP, the release of receptor ligands coupled with G proteins such as bradykinin, adenosine, and opioids leads to ERK1/2/phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) activation. The further activation of protein kinase C (PKC) may occur both downstream of Akt and through the signaling pathway of the phospholipase, as happens in the case of the activation of the A1 adenosine receptor (33, 34, 192). Tyrosine kinase receptors are likely to be involved through transactivation of the Epidermal Growth Factor receptor, which, in turn, activates PI3K/Akt. Thereafter, phosphorylation and other intracellular signaling such as nitrosylation and O-linked glycosylation may involve multiple targets. Activated Akt can, in turn, phosphorylate/activate other kinases, including endothelial NOS (eNOS), resulting in activation of the NO/guanylate cyclase/protein kinase G (PKG) pathway. Glycogen synthase kinase 3b (GSK-3b) is also involved after its phosphorylation/inactivation, thus preventing its actions on mPTP opening (9, 62). Akt and GSK-3b also play a protective role against apoptosis. They are, indeed, able to phosphorylate/inhibit pro-apoptotic factors (Bax and Bad) and to phosphorylate/activate anti-apoptotic factors (Bcl-2 and p70s6K), which, in turn, are able to block some pro-apoptotic factors. PKG is another kinase involved in cardioprotection that carries out its activity at different levels: activating PKC, inhibiting mPTP by enhancing the production of NO, and reducing Ca²⁺ overload by inhibiting the sarcoplasmic reticulum protein phospholamban, thus favoring the reuptake of Ca²⁺. The activation of PKC and its role in the cardioprotection may depend on different signal pathways. PKC can be directly phosphorylated/activated, whereas the mitochondrial kinase isoform is PKG dependent. PKG exerts its protective action at different levels, by inhibiting the opening of mPTP or through the opening of the mitochondrial ATP-dependent potassium channels (mKATP) (83), the alkalization of the mitochondrial matrix, and the production of signaling molecules such as ROS and reactive nitrogen species (RNS) (33, 141). The cardioprotective reactive species ROS/RNS are produced in the short I/R cycles of the IP protocol (70). These radical species exert their protective activity through post-transductional modifications, in particular nitrosylation. In addition, they can also determine the activation of other kinases, such as p38-MAPK and JAK/STAT (129, 141). The link between ROS/PKC (in particular, the PKC ϵ 2 isoform) was studied in rabbit hearts, in which a pharmacological IP was induced while administering free radicals generated by purine/xanthine at the coronary level. Under these conditions, the simultaneous administration of a PKC inhibitor (polymyxin B) causes the loss of cardioprotection (179). The phase of protection afforded by IP is long-lasting: It is, in fact, recognized late, with very slow development (about 6–12h after the preconditioning protocol), but with a decidedly longer

duration in terms of protection (“late IP,” lasting about 3–4 days) (16). This late phase of the IP requires changes in the transcription of cardioprotective protein genes. Among these, the signal transducer and activator of transcription 3 (STAT3) seems to be fundamental for IP cardioprotection. Indeed, cardiomyocytes isolated from STAT3-null mice are not protected by IP (15, 68). Collectively, the kinases involved during reperfusion are part of the so-called Reperfusion Injury Salvage Kinases (RISK) and Survivor Activating Factor Enhancement (SAFE) pathways (72). Similar pathways are involved in the PostC protection. The pharmacological protection is obtained by the infusion of drugs that are able to activate protective pathways such as RISK or SAFE, or NO/GMPc/PKG, similar to what occurs after the “classical” IP or PostC maneuvers, before or after the ischemia (136). Pharmacological protection can be obtained by administering substances of either endogenous (adenosine, bradykinin) or exogenous origin such as diazoxide or anesthetics (isoflurane). The inhibitor of mPTP Cyclosporin A, recently used during reperfusion as a PostC agent, is of particular interest in the clinic (9). The mitochondrial KATP channels also play an important role in PostC, being involved in maintaining the closure of the mPTP (129). Similar to preconditioning, autacoids can trigger a complex protective signaling pathway, including RISK and SAFE signaling (67, 71, 73, 97, 135, 138, 139, 144–146, 168, 180). Although not all studies confirm their role (170), the PI3K/ Akt pathway and ERK1/2 are also reported to be involved in this response. See Table 1 for a summary. Another important aspect relative to cardioprotection is the acidosis that is maintained during the ischemia by inhibition of the ATPase pump. Indeed, during the PostC maneuvers, the persistent acidosis contributes to limit the mPTP opening and, additionally, favors kinase activation (34, 57, 84, 85). Although its location in the signaling cascade is unclear, PKC ϵ and PKG may also participate in PostC. Another possible mechanism taking part in PostC involves transient modification of redox conditions (144). The PostC protection is abolished when ROS scavengers (such as NAC and N-(2-mercapto-propionyl)glycine [MPG]) are administered during PostC maneuvers (135, 138, 144, 180). In addition, PostC determines intermittent oxygen bursts at the mitochondrial level, allowing the production of ROS, in a phase in which the enzymes responsible for the synthesis of large quantities of ROS are not yet reactivated. During PostC maneuvers, changes in the activity of many antioxidant enzymes have been highlighted (143). The mechanisms listed so far participate in the closure of mPTP, including the Bad/Bax and Pim-1 systems, correlated with the cardioprotection from PostC through the prevention of the mPTP opening and reduction of mitochondrial swelling (142). Finally, also the extracellular vesicles (EVs), which play an important role as carriers of protective molecules (e.g., miRNAs or proteins), might contribute to improve cardiac function after I/R. EVs can be secreted from almost every cell type in the human body (e.g., endothelial cell, platelets) and can be transferred via the bloodstream in almost every compartment (41, 187).

Remote preconditioning

A further cardioprotective protocol, able to reduce the damage caused by I/R, is the remote ischemic conditioning (RIC), which consists of short cycles of I/R in an organ or tissue at a distance from the heart (Fig. 2). In particular, RIC can be considered as Pre-, Per-, and Post-C, when these short I/R procedures are performed, before or during cardiac ischemia and after reperfusion, respectively (79, 160). Clinical trials showed that RIC is able to reduce acute myocardial ischemia or increase myocardial salvage in patients with ST segment elevation myocardial infarction treated by primary percutaneous coronary intervention (71). The signal transduction mechanism involved in RIC is unclear in its details. The intramyocardial signal transduction of RIC is similar to that of classical conditioning protocol (IP and PostC maneuvers) (92), but the transfer signal from the remote tissue or organ to the heart or other target organs is unknown (80), and the different neuronal and humoral mechanisms reported in literature appear to be casually involved (79, 160). It has been proposed that the anti-apoptotic effect of RIC is induced by the release of EVs containing miR-24, which in a paracrine manner plays a central role in the protective effects of RIC (60, 119). Although it has been recently suggested that EVs represent an important mediator of RIC, further molecular and in vivo experimentations are necessary to clarify their role in RIC.

Exercise-Induced Preconditioning (Animal and Human Models)

The possibility to mimic IP is one of the various mechanisms through which physical exercise potentially confers cardioprotection. IP classically refers to the capacity of short episodes of sub-lethal ischemia to render the myocardium more resistant to subsequent, more prolonged, ischemic insults (124). This phenomenon was first described in dogs by Murry et al., who found that IP could substantially reduce infarct size (124). They also reported that this effect was unrelated to the development of collateral flows. Of note, after this original observation in dogs, many authors reproduced the infarct-sparing effect of IP in several mammals, such as rats, mice, rabbits, swine, and goats (59, 194). Along the reduction in infarct size, IP has also been demonstrated to protect the heart against damage caused by ischemia–reperfusion (133) and to improve vascular and coronary reactivity (59). Of note, several evidences suggest that exercise can confer cardioprotection in a manner that resembles the IP effect without the necessity of previous ischemia, that is, the protection provided by exercise does not require the application of ischemia directly to the heart itself. This has been demonstrated in a consistent number of investigations conducted in animal models, whereas there is only limited and indirect evidence that exercise can mimic the effects of IP in humans (112).

Animal studies

Consistent effects of training on the reduction of infarct size were several times reported in rats and in mice. This effect has been attributed to IP-like effects and it could be obtained with different

exercise types, such as long-term or short-term endurance training, resistance training, interval training, and even by a single bout of exercise (23–25, 29, 56, 155, 188). Of note, it has been reported that the acceleration in myocardial metabolism due to tachycardia confers cardioprotection similar to that induced by IP. However, this was obtained without the need of ischemia (47, 93). Hence, tachycardia alone can directly precondition the heart by activating myocardial cells metabolism. A further interest

ing observation was that the infarct-sparing effect due to exercise-induced tachycardia was greater than that observed with tachycardia alone, thereby suggesting that during exercise stimuli other than increased myocardial metabolism alone trigger IP (46). Exercise was also demonstrated to be able to limit heart damage due to I/R. Investigation in isolated hearts from trained rats reported that the recovery of cardiac functions after global ischemia was greater compared with hearts obtained from sedentary animals (22). These results are in line with other observations demonstrating that endurance training improves myocardial functions during I/R (43, 152). In summary, numerous data have been published indicating that in various mammal species IP may be induced in a nonischemic way, namely by exercise or tachycardia. Therefore, the concept that heart conditioning can be reached by exercise appears to be based on a solid scientific background.

Human studies

Since experimentally induced ischemia or infarction is not a feasible option in humans, in vivo research to test directly whether exercise-induced IP can effectively protect the human heart from infarction cannot be conducted. However, there are several indirect clues suggesting that the human heart can be actually preconditioned by exercise. Specifically, observations during repeated exercise tests performed in patients with stable angina demonstrated that exercise can effectively protect the heart from ischemia. In particular, the warm-up (WU) phenomenon, which refers to the enhanced exercise performance and the reduced signs and severity of angina shown by some patients with coronary disease a few minutes after a previous effort, has been attributed to a preconditioning-like effect. It has been reported that the degree of myocardial stunning after exercise-induced ischemia was attenuated if the patient had previously exercised (157). Moreover, myocardial O₂ consumption was reduced during WU in comparison with the first effort (126). These findings suggest that WU improves myocardial performance and metabolism during subsequent efforts. However, there is the possibility that the opening of collateral flows, with coronary vasodilation, is responsible for the WU, although some authors have argued against this possibility and demonstrated that the protection afforded by exercise induced ischemia was independent from collateral flow recruitment (98). It should be also highlighted that improved exercising capacity and reduced signs of ischemia can still be present 24 to 48h after ischemic exercise, when collateral flows should already be closed. This

observation is consistent with the time course of the second window of protection (SWOP) afforded by IP, that is, a kind of protection triggered by IP that requires protein transcription to be effective (98). In support of this finding, there are studies showing that patients with coronary insufficiency, who underwent a sequence of repetitive exercise tests, exhibited improved myocardial performance measured with thallium-scintigraphy during the last of the sequential efforts (116). This observation was confirmed by other investigations conducted in patients with stable angina demonstrating that, together with the reduced ischemic signs, global hemodynamic was also improved during exercise performed 48h after a previous exercise-induced ischemia (37). Further, by employing a sequence of repeated treadmill efforts, it was shown that signs of the presence of cardioprotection (reduced ST segment depression, increased rate pressure product, and longer onset of chest pain) disappeared 6h after a session of exercise-induced ischemia to reappear again after 24h, which again is consistent with the time course of the SWOP (131). In this regard, it should, however, be acknowledged that one study failed to demonstrate the possibility of inducing the SWOP with exercise-induced ischemia in humans (178). Overall, all these observations indirectly support the notion that the human heart can be preconditioned by exercise, although it should be underscored that all the evidence demonstrating this possibility derives from studies on patients with coronary disease, in whom the preconditioning effect is triggered by exercise-induced myocardial ischemia. Differently, the attempt to enhance cardiac performance in healthy subjects by means of a sequence of maximal tests on a cycle ergometer failed, and this suggests that ischemia must occur to detect any preconditioning effect due to exercise (36). Hence, the capability of exercise to mimic IP without the occurrence of ischemia is still to be demonstrated in humans. Importantly, to the best of our knowledge there are no studies in humans that have dealt with the effects of regular exercise training programs, which are usually conducted at sub-maximal and sub-ischemic threshold intensity. To date, there are only retrospective studies demonstrating that greater levels of physical capacity in the week preceding an infarction were associated with lower mortality and more nonfatal cardiac events (156). Moreover, it was reported that exercise in the week before a coronary bypass grafting increased the rates of survival (1). Hence, there is no available information on thresholds for exercise duration and intensity to reach the beneficial effects of preconditioning induced by exercise. In this regard, specific studies designed to investigate on this possibility and to establish at which intensity effort should be performed to trigger the preconditioning phenomenon are needed.

Biological Mechanisms Involved in the Protective Effect of Exercise Against Heart Failure

As previously exposed, animal studies have demonstrated reduced necrosis and improved myocardial function after ischemia following exercise training. Although mechanisms responsible for the supposed exercise-induced cardioprotection remain elusive, there are some putative cellular

adaptations due to exercise that may help in explaining the phenomenon. Specifically, some investigations have shown that exercise training increases the expression of sarcolemmal ATP-sensitive K⁺ channels, which are involved in the classical form of IP (23, 199). Moreover, other studies in rats and dogs have demonstrated that blocking both sarcolemmal and mitochondrial ATP-sensitive K⁺ channels resulted in the abolition of the training-acquired cardioprotection (24, 46, 86), although to date it is not clear whether both types of channel are necessary for cardioprotection. Other putative mechanisms are related to the production of several metabolites such as adenosine (46), bradykinin (183), and opioids (118) which are released by the contracting myocardium during effort. These metabolic by-products are known to accumulate during ischemia, but they are also released during moderate-sustained exercise and this may explain why, in animal models of preconditioning, exercise was found to be able to trigger IP without the need of ischemia. Actually, it has been proposed that a single episode of moderate sub-maximal physical exercise, which unlikely induced myocardial ischemia, was able to induce cardioprotection in rat hearts. Authors explained this cardioprotection with a PKC-mediated mechanism, since pharmacological inhibition of this enzyme abrogated cardioprotection (190). This observation demonstrates that ischemia is not a prerequisite for the activation of the IP biochemical cascade and that the PKC is directly modulated by exercise. Another important substance that may play an important role in exercise-induced preconditioning is NO. This substance is pivotal in the cardioprotection afforded by IP as it triggers and mediates both the first and the SWOP. Indeed, exposure to NO donors can reproduce the effects of IP in the absence of ischemia (37, 88). It has been observed that exercise increases NO production by increasing shear stress (99). Hence, it was hypothesized that exercise-induced increase in NO production is a potential mechanism by which physical training induces cardioprotection. A number of experimental evidences confirm this hypothesis. In the mouse heart, the reduced extension of infarct size induced by training was accompanied by both eNOS activation and increased expression of inducible NOS (iNOS). The effects of training, including the upregulation of iNOS, were absent in eNOS(-/-) knockout mice. Similarly, exercise-induced cardioprotection did not occur in iNOS(-/-) mice or after treatment with a selective iNOS inhibitor, suggesting that iNOS plays an important role in exercise-induced cardioprotection (3). A further study in mice showed that the reduction in the infarct size, and the expression and activity of eNOS persisted till 7 days after training accomplishment. Other studies showed that the β_3 adrenergic receptors, at least in part, mediate the enhanced activation of eNOS and production of NO within the heart during exercise, thus suggesting the involvement of the adrenergic system in cardioprotection (25). In dogs subjected to I/R, the cardioprotective effect of acute exercise of increasing intensity was blunted by inhibitors of iNOS such as aminoguanidine and AEST, or by the nonselective NOS inhibitor N(x)-nitro-L-arginine methyl ester (LNAME).

Interestingly, the cardioprotective effect was reduced both by LNAME administered before exercise and by AEST given before coronary artery ligation, thus indicating that NO exerts cardioprotective effects both early and late after exercise (69). It must also be taken into consideration that, in addition to NO produced inside the heart, skeletal muscle also generates RNS, such as NO or nitrite ion (173), high doses of which cause nitrosative stress and tissue damage, whereas low doses may exert beneficial effects on cardiac cells. ROS production is augmented by exercise (51), and this may be another potential exercise-related mechanism underlying cardioprotection. Actually, PKC is directly activated by ROS generation, that is, without the need to interact with a specific receptor (194). Moreover, habitual physical activity upregulates myocardial antioxidant capacity because of the sustained oxidative stress. This is testified by the increased myocardial levels of manganese SOD and of extracellular SOD (116, 191). The upregulation of these enzymes is involved in the SWOP, thereby providing another potential mechanism by which exercise protects from ischemia. In view of the fundamental role of ROS in I/R injury (122), several studies were performed to investigate whether the cellular antioxidative defenses are involved in exercise induced cardioprotection. The production of ROS occurring both in mitochondria and in the cytosol may be counteracted by the antioxidative defense system, which includes several enzymes, such as the different form of SOD present in the cytosol or in the mitochondria, catalase, glutathione, glutathione peroxidase and glutathione reductase, and thioredoxin reductase (61). It has been shown that both short- and longterm exercise training enhances the activity of mitochondrial matrix form–manganese [Mn] SOD (MnSOD) within the heart, whereas low-intensity exercise is ineffective. Data obtained by using antisense oligodeoxy ribonucleotide against MnSOD are partially conflicting: Some studies showed that this treatment prevented the reduction in the infarct size induced by exercise training, whereas another report indicated it was ineffective in the development of myocardial stunning after I/R. At present, the role of the cytosolic isoform of SOD in the exercise-induced cardioprotection has not been established (151). Data regarding catalase, glutathione peroxidase, and glutathione reductase suggest a minor or no role of these enzymes in cardiac adaptation after exercise (61). Administration of MPG, a free radical scavenger, before exercise did not affect the external work output of the heart of trained animals (174). The lack of uniformity of these results can be tentatively explained with the fact that, although it is generally accepted that ROS play a fundamental role in I/R injury, they can also act as a double-edged sword, being also able, at least at low concentrations, to participate in the cascade of events that lead to cardioprotection (105, 122). Exercise can also increase the expression of proteins involved in the cardioprotection afforded by IP. Specifically, HSPs, which are a group of proteins whose production is stimulated by stress stimuli, have been found augmented up to three times in the myocardium in response to physical training (106). It is believed that HSPs, in particular HSP72, can

protect cells from a variety of stressful conditions, including ischemia–reperfusion (82, 154). However, their contribution to the cardioprotection afforded by exercise remains controversial since the cardioprotection lasts longer than the HSPs' half time (101, 175). In addition, despite the fact that the production of HSP72 within the heart depends on environmental conditions, being several-fold enhanced after exercise in room temperature, but unaltered by exercise in cold, the cardioprotective effect of exercise is similar in both conditions (154, 175). Recent data suggest that HSP70 also participates in exercise preconditioning. HSP70 is upregulated after exercise and may exert a cardioprotective role through its capacity to repair unfolded proteins or to stabilize endoplasmic reticulum functions (196). Other intracardiac factors involved in exercise-induced preconditioning include KATP channels, mitochondria, lipid mediators, and polyamines. An early study performed by Brown et al. (23) in endurance trained rats showed that blockade of sarcolemmal KATP (sKATP) channels abolished the training-acquired cardioprotection, whereas blockade of mKATP channels had no effect, thus suggesting an important role of sKATP channels in cardioprotection. Further studies performed on dogs in which early and late cardiac preconditioning were induced by acute high intensity exercise before and 24h before coronary occlusion showed that both the early and the late conditioning depend on mKATP activation (132). The role of KATP channels in exercise-induced cardioprotection has been recently confirmed by the fact that blockade of mKATP channels reduced the protective effect induced by RIC on infarct size and arrhythmias on the isolated rat heart (86). Endurance training promotes the development of a mitochondrial phenotype resistant to I/R injury, leading to a decrease in ROS production and in the rate of opening of mPTP, as well as to an increase in tolerance to high calcium level and in the amount of antiapoptotic proteins (4,54,100,153). Both long-term endurance and short-term trainings were shown to increase resistance of the mPTP opening during I/R in rats (110, 111) and mice (150). The fact that training did not influence the heart function and coronary flow (32) suggests a direct action on mPTP features, even if we are not aware of data regarding their response to acute exercise. Proteomic studies indicate that several changes induced by endurance exercise training in mitochondrial proteins involved in amino acid and fatty acid metabolism, citric acid cycle and electron transport chain, creatine kinase phosphorylation pathway, and oxidation–reduction processes may participate to determine the improved outcomes in the heart undergoing I/R (89, 107). Although it is feasible that the ability to maintain ATP homeostasis could contribute to cardioprotection induced by exercise, there is no direct evidence connecting these processes to adaptation to exercise. On the other hand, several experimental evidences suggest a direct link between exercise, oxidation–reduction balance, and cardioprotection. As previously mentioned, endurance exercise training increases the presence of SOD and glutathione reductase activity in myocardiocytes (55), thus enhancing the presence of

antioxidants that protect mitochondria against increased ROS production induced by I/R. In addition, endurance exercise training also reduces the presence of monoamine oxidase A in both subsarcolemmal and intermyofibrillar mitochondria in the rat heart (90), thus possibly leading to reduced production of H₂O₂ and apoptosis in cardiac myocytes undergoing I/R. Ceramide and sphingosine-1-phosphate (S1P) are bioactive sphingolipids involved in I/R injury and cardioprotection. IP is able to limit the increase of ceramide content occurring in the I/R heart (13), which is, at least in part, responsible for apoptosis of cardiomyocytes (19). Although no direct measurement of ceramide content in the I/R heart of trained animals has been performed, the fact that acute exercise reduces the heart content of ceramide in the rat (45) suggests a possible role for this mediator in cardioprotection. The S1P exerts beneficial effects against I/R injury, being involved in both IP and PostC in the I/R heart. Although, at present, no data regarding the content of S1P in the heart after exercise are available, the fact that plasma levels of S1P increase in untrained healthy humans after acute exercise suggests that S1P may participate in cardioprotection induced by exercise (12). It is conceivable that other lipid mediators contribute to exercise-induced cardioprotection. For instance, it has been shown that platelet-activating factor (PAF) production within the heart participates in the induction of IP, by inducing the activation of kinases included in the RISK pathway. The fact that low increases in plasma PAF concentrations occur in humans during exercise also suggests that this mediator may be involved in exercise-induced cardioprotection (134). Although being a powerful way to protect the heart from I/R-induced damage, IP has shown to be ineffective in aged hearts. Since exercise training decreases the incidence of age-related cardiovascular dysfunctions and upregulates the ornithine decarboxylase (ODC)/polyamine pathway, Wang et al. (184) investigated whether exercise can restore IP protection in aged rat hearts and the role of polyamines in this phenomenon. Although IP did not affect the metabolism of polyamine, exercise training restored both the effectiveness of IP and the polyamine pool by activating ODC and inhibiting the spermidine/spermine acetyltransferase enzyme in aged hearts. In addition, exogenous polyamines improved mitochondrial dysfunction associated with age. The phenomenon of “remote preconditioning” should be also considered, which refers to the possibility to precondition the myocardium by inducing ischemia in a remote organ or tissue. Several investigations have demonstrated that transient ischemia in small intestine, kidney, and skeletal muscle effectively induces cardioprotection (14, 165, 185). It has been hypothesized that remote preconditioning is initiated by humoral factors produced by the ischemic tissue (such adenosine and bradykinin), which are released into the blood and then transferred to the myocardium where they trigger the cardioprotection, although the exact mechanisms involved in this phenomenon are still unknown (112, 188). In this regard, it is to be considered that the skeletal muscle is a very active secretory

tissue and that several products of its metabolism, such as myokines, opioids, NO, and by-products of the anaerobic metabolism (lactate, adenosine diphosphate [ADP], adenosine, etc.) are continually produced by the contracting muscle and released into the blood during exercise, even in the absence of any ischemic condition. Among myokines, particularly important is IL-6. Studies performed on IL-6 knockout mice highlighted the role of IL-6 in the exercise-induced heart preconditioning. Although as expected, exercise exerted a protective effect against I/R induced arrhythmias and reduced infarct size in wild animals, it was ineffective in IL-6 knockout mice (115). Although, at present, the data on the cardioprotective effect of other myokines are scarce, their role in exercise-induced heart preconditioning appears a very promising area of research. The involvement of opioids in exercise-induced cardioprotection has been suggested by the blocking effect of naloxone or other opioid receptor antagonists (44, 118). The use of selective blocking agents suggested that exercise-induced preconditioning is mediated by delta-opioid receptors. A long-term training was able to reduce the infarct size over three times in rats undergoing I/R, and this effect was prevented by naloxone or by naltrindole, a selective delta-opioid receptor blocker (18). The fact that left ventricle mRNA of proenkephalin was enhanced immediately after and 120min later than exercise indicates that both the blood-borne and intracardiac opioids can participate in the exercise-induced preconditioning (118). Hence, it can be hypothesized that these metabolites may induce remote preconditioning without the need of ischemia at cardiac level, and this may explain, at least in part, the cardioprotective effect of exercise. To the best of our knowledge, this hypothesis has never been verified although some indirect proofs have been found in support of this possibility. In detail, recent research demonstrated that dialysated plasma from humans undergoing high-intensity exercise reduced infarct size in isolated rabbit hearts after ischemia–reperfusion injury. This cardioprotective effect was similar to that induced by plasma from humans exposed to RIC (117). Authors of the quoted study suggested that exercise-induced cardioprotection was at least partially mediated by the release of one or more humoral factors. Similar results were obtained in mice hearts perfused with dialysated plasma from highly trained humans (swimmers) undergoing a protocol of ischemia–reperfusion exercise (87). Along with its cardioprotective effects, RIC has also been found able to improve endothelium-dependent function after strenuous. This effect has been attributed to humoral mechanisms that increased the activation of KATP channels and the concentration of NO (109). Of note, it has been observed that IP induced by intermittent upper-arm ischemia performed before primary percutaneous coronary intervention could attenuate reperfusion injury in patients with evolving myocardial infarction, thereby resulting in the reduction of myocardial damage (20). Others have proposed that remote preconditioning works through a neural pathway between the nervous tissue and the heart (104). Indeed, stimulation of sensory nerve endings in the ischemic area may

elicit RIC of the heart. Although the precise mechanism of this phenomenon is not clear, it has been shown that both parasympathetic and sympathetic efferent pathways to the heart seem to be involved (48, 81). It has been hypothesized that the changes of metabolic environment could activate sensory receptors within contracting skeletal muscle, leading to IP. On the other hand, muscular exercise enhances the activity of the adrenergic nervous system, leading to tachycardia and increased inotropism of the heart. The role of the adrenergic system in cardioprotection has been previously discussed in relation to NO. Although interesting, to our knowledge the possibility that the nervous system also may participate in remote preconditioning has never been definitively proven and nervous segments potentially involved have not been identified. Taken together, the studies performed on humans or in animal models suggest that exercise-induced cardioprotection is a multifactorial phenomenon, depending on both extracardiac and intracardiac factors. Working together, all these factors may activate cellular pathways widely shared with those involved in classic preconditioning and remote conditioning, such as components of the prosurvival (RISK) pathway such as Akt, PKCe, and ERK1/2 (108). The major putative mechanisms responsible for the exercise-induced IP are shown in bF4 Figures 4 and bF5 5 and reviewed in Refs. (2, 17, 31, 52, 94, 112, 153, 176, 188).

Exercise and Cardioprotection Against Cardiotoxicity Due to Antiblastic Drugs

Although advances in early detection and therapy have led to significant improvements in longevity after a cancer diagnosis, patients with early-stage disease not only remain at high risk of cancer recurrence but also remain at risk for late effects caused by adjuvant therapy, in particular cardiovascular disease (CVD) due to the cardiotoxic side effects of treatment. Anthracyclines are powerful chemotherapeutic drugs widely used in the treatment against several kinds of neoplasms in both children and adult populations. However, anthracyclines induce both early and late cardiotoxic effects: More than 2% of patients treated with doxorubicin (DOX) undergo heart failure, with a mortality rate more than 60% at 2 years. Several evidences indicate that physical exercise, a correct lifestyle, and the control of risk factors can, at least partially, reduce anthracycline-induced cardiotoxicity. In particular, exercise training represents a feasible nonpharmacological treatment that is able to improve cardiovascular and endothelial functions, to regulate proapoptotic signaling, to protect against ROS, and to decrease autophagy/lysosomal signaling (21, 29, 91, 125, 162) (F6 c Fig. 6). Cardiac dysfunctions induced by chemotherapy are characterized by reduction of left ventricular ejection fraction, in the presence or not of heart failure (53). These alterations are attributed to production of ROS and oxidative stress, alterations in mitochondrial metabolism and lysosomal structure and function. Anthracyclines also impair iron metabolism, promoting its accumulation within cardiac myocytes (95). However, several factors, such as cumulative dosage, associated use of other drugs, age and female gender, as well as the possible presence of cardiac hypersensitivity

reactions, can concur to worsen anthracycline cardiotoxicity. Several clinical studies assessed the benefits of exercise against heart failure induced by chemotherapy. Aerobic training improved VO₂max and decreased heart rate, systolic and diastolic blood pressure in patients undergoing treatment for cancer (182). A study assessing the effect of exercise during and after treatment showed that the group of patients undergoing a prescriptive exercise program had maximal benefit in terms of cardiopulmonary parameters and fatigue levels, suggesting the beneficial effect of an early exercise intervention (161). Patients can also benefit from supervised or home-based exercise regimen in the post-treatment period (40, 148). In addition, a combined aerobic and resistance exercise protocol improved exercise tolerance and flexibility variables in cancer survivors (172). However, other studies have yielded conflicting results. The fact that exercise did not prevent ventricular remodeling when trastuzumab was used as associated therapy suggested that not all the molecular targets involved can be affected by exercise (75). In another study, the best benefit was observed in the self-directed exercise group patients, whereas supervised exercise had beneficial effects only in patients not under chemotherapy (163). A recent report by Bourdon et al. (21) has been devoted toward analyzing the effect of aerobic exercise on cardiopulmonary fitness in childhood cancer survivors who are under treatment or had been treated with a cardiotoxic agent. Although meta-analysis of the nine included studies shows that aerobic exercise exerts a significant positive effect, subgroup analyses of clinical characteristics and exercise variables gave no significant findings. Although this analysis gave no definitive results, it represents an initial step to establish the possible protective effect of aerobic exercise against cardiotoxicity consequent to cancer treatment. Several studies in humans and in animal models have been performed to elucidate the possible cellular basis of exercise-induced changes in CVD induced by chemotherapy. The cardiotoxicity of anthracyclines is, in general, attributed to enhancement of ROS production, leading to mitochondrial dysfunction, peroxidation of several substrates, and increased apoptosis, finally resulting in cell dysfunction and death. Aerobic exercise can counteract these effects, causing enhancement of antioxidant and anti-apoptotic capacity. A possible protective mechanism involves cellular pathways depending on gp130 cytokines and neuregulin-1 (NRG1), a paracrine mediator produced by microvascular endothelial cells, which is upregulated in heart failure and has significant prognostic value for this pathology (96). It has been shown that exercise is opposed to the alterations of NRG1/ErbB signaling as well as to enhancement in angiotensin II and adrenergic agonists levels through the increase of mechanical stress and depression of the neurohormonal system. In addition, exercise can increase myocardial Akt, thus reducing pathological LV remodeling and hypertrophy (38, 162). On the other hand, being able to upregulate vascular endothelial growth factor (VEGF) production and endothelial progenitor cells activation, exercise may counteract the action of drugs that exert antiangiogenic effects by targeting

VEGF receptor or acting as tyrosine kinase inhibitors (162). Studies conducted on animal models confirmed the protective effects of exercise against cardiac alterations induced by chemotherapeutic drugs, and they allowed to clarify some of the cellular mechanisms involved in its positive effects. Moderate-term endurance training before treatment with DOX enhanced cardioprotection markers (HSP70, SOD) and reduced cardiotoxicity in heart tissue (166). Exercise training provided cardioprotection against delayed-onset cardiotoxicity also when treatment was initiated in childhood, as shown by assessing cardiac function in rat pups treated with DOX, which remained sedentary or were allowed to voluntarily exercise for 10 weeks (76). Smuder et al. (171) tested the involvement of altered cardiac gene and protein expression of mediators of the autophagy/lysosomal system in cardiac alterations induced by DOX. The major finding of this study is that exercise training is able to reduce the increase of both mRNA and protein levels of numerous key autophagy genes caused by DOX treatment, thus suggesting that the protective effect of exercise may be, at least in part, related to its ability to reduce increases in autophagy signaling induced by DOX. Several studies show that exercise performed before DOX treatment is able to reduce mitochondrial toxicity in cardiac cells. In particular, the effects of two different (endurance treadmill training [TM] and voluntary free-wheel activity [FW]) exercise models applied before and during DOX treatment were evaluated in male young Sprague-Dawley rats (113). DOX treatment induced ultrastructural and functional mitochondrial alterations and decreased oxidative phosphorylation proteins. Moreover, DOX decreased the content and activity of complex I, mitochondrial biogenesis (mitochondrial transcription factor A [TFAM]), and increased acetylation and oxidative stress. Although TM prevented all the alterations induced by DOX, FW was not able to prevent the decreases in TFAM and SIRT3, a protein involved in mitochondrial oxidative stress. Moreover, both TM and FW prevented the increased mPTP susceptibility and apoptotic signaling, the alterations in mitochondrial dynamics, and the increase in auto(mito)phagy signaling induced by DOX (114). The study of Lien et al. (102) highlighted some cellular mechanisms involved in the protective effect of chronic exercise training against DOX-induced cardiotoxicity. Exercise preconditioning attenuated both in vivo and ex vivo cardiac dysfunctions. In particular, when compared with sedentary animals, both TM and FW preserved fractional shortening, left ventricular developed pressure, and the expression of sarco endoplasmic reticulum calcium-ATPase 2a protein. These findings suggest that pretreatment with endurance exercise may be a potentially useful strategy to improve myocardial tolerance against DOX-induced oxidative damage, in particular maintaining mitochondrial function and calcium handling in cardiomyocytes.

Conclusions

Several evidences indicate that exercise acts as a physiological stress that is able to induce a defensive phenotype in the heart, exerting a cardioprotective effect and reducing cardiac dysfunction and infarct size after I/R. Although the precise mechanisms underlying this effect have not yet been fully clarified, much progress has recently been made in understanding this phenomenon. Exercise induced cardioprotection depends on the production of several cellular mediators and shares the same intracellular pathways that are responsible for the “classical” conditioning of the heart, such as RISK and SAFE. Interestingly, exercise-induced preconditioning largely depends on factors originated from contracting skeletal muscles, which therefore “take care” of the heart (remote conditioning). The same factors also seem to be responsible for the ability of exercise to improve myocardial tolerance against DOX induced oxidative damage. Although to date a direct demonstration that exercise can condition the heart of healthy individuals is lacking, a preconditioning effect induced by ischemia has been observed in patients suffering from coronary disease (“warmup” phenomenon). Thus, regular exercise should be recommended not only to achieve beneficial effects by reducing cardiovascular risk factors but also because it appears to be the only available practical method to induce IP of the heart. In conclusion, although the results obtained from animal models and human studies are encouraging, rigorous investigations are still required to clarify the role of physical exercise in preventing I/R damage and cardiovascular toxicity of chemotherapy. In particular, future investigations are required to define the proper intensity, duration, and frequency of exercise for prevention of cardiotoxicity caused by the various chemotherapeutic regimens that are currently applied.

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LIST OF ABBREVIATIONS

CVD: cardiovascular disease

DOX: doxorubicin

eNOS: endothelial NOS

EVs: extracellular vesicles

FW: voluntary free-wheel activity

GSK-3 β : glycogen synthase kinase b

HSPs: heat shock proteins

IL-6: interleukin-6

iNOS: inducible NOS

IP: ischemic preconditioning

I/R: Ischemia/Reperfusion

LNAME: N(ω)-nitro-L-arginine methyl ester

mK_{ATP}: mitochondrial ATP dependent potassium channels

MnSOD: mitochondrial matrix form –manganese [Mn] SOD

MPG: N-(2-mercaptopropionyl)glycine

mPTP: mitochondrial permeability transient pore

NO: nitric oxide

NOS: nitric oxide synthase

NRG1: Neuregulin 1

ODC: ornithine decarboxylase

ONOO⁻: peroxynitrite

PAF: Platelet-activating factor

PI3K: phosphatidylinositol 3-kinase

PKC: Protein Kinase C

PostC: ischemic post-conditioning

RIC: remote ischemic conditioning

RISK: Reperfusion Injury Salvage Kinases

RNS: reactive nitrogen species

ROS: reactive oxygen species

S1P: sphingosine-1-phosphate

SAFE: Survivor Activating Factor Enhancement

sK_{ATP}: sarcolemmal K_{ATP}

STAT3: signal transducer and activator of transcription 3

SOD: superoxide dismutase

SWOP: second window of protection

TFAM: mitochondrial transcription factor A

TM: endurance treadmill training

VEGF: vascular endothelial growth factor

WU: warm-up

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Table 1. Endogenous factors involved in cardioprotection

Substance	Time of Administration	of I/R Injury	Clinical trials	References
<i>G protein-coupled receptors (GPCRs) activators</i>				
Adenosine	Pre and Post	↓	Yes	32, 33, 42, 47, 59, 94, 192
Adipocytokines	Pre and Post	↓	None	82
Bradykinin	Pre and Post	↓	Yes	138, 139, 183
Glucagon-like peptide	Pre and Post	↓	Yes	140, 197
Obestatin	Post	↓	None	6, 146
Opioids	Pre and Post	↓	None	44, 77, 118, 119
PAF	Pre	↓	None	134
GHRH	Pre and Post	↓	None	64
<i>Tyrosine kinase receptor activators</i>				
Erythropoietin	Pre	↓	Yes	121, 159
Thrombopoietin	Pre and Post	↓	None	11
Insulin	Pre	↓	None	10, 164
<i>Growth factors</i>				
Neuregulin	Pre and Post	↓	Yes	49, 97, 122
Ghrelin-associated peptides	Pre and Post	↓	None	29
<i>Guanylyl cyclase(GC)-linked receptor activators</i>				
Natriuretic peptides	Pre and Post	↓	Yes	38, 193
<i>Agents Acting on Intracellular Pathways</i>				
NO, CO, H ₂ S	Pre and Post	↓	Yes	3, 8, 25, 36, 41, 50, 59, 69, 88, 128, 135, 173

Agents with unknown membrane target					
Chromogranin derived peptides	A-	Pre and Post	↓	None	26, 147
Exosomes and microvesicles	and	Remote PreC	↓	None	40, 60, 187

FIGURE LEGENDS

Figure 1. Ischemia-reperfusion injury: schematic representation of molecules involved in the I/R damage. ATP: Adenosine-5'-triphosphate; Cyt_c: Cytochrome c; mPTP: mitochondrial permeability transition pore; RNS: reactive nitrogen species; ROS: reactive oxygen species; SR: sarcoplasmic reticulum; TNF α : Tumor necrosis factor- α ; $\Delta\psi$: mitochondrial membrane potential.

Figure 2. Schematic diagram showing the time-course of typical protocols of ischemic cardioprotection. The parts signed in black indicate periods of ischemia.

Figure 3. Schematic representation of the RISK and SAFE cardioprotective pathways. mPTP, mitochondrial permeability transition pore; mK_{ATP}, mitochondrial potassium ATP dependent channel.

Figure 4. Putative mechanisms responsible for exercise-induced preconditioning. Exercise directly induces the classic form of preconditioning at heart level by means of tachycardia, opening of ATP-sensitive K⁺ channels, metabolites, and protein production. Muscle activity induces remote preconditioning by means of metabolites and myokines production and, possibly, by the activation of neural pathways still to be identified. See text for more details.

Figure 5. Schematic overview of cellular reprogramming in cardiomyocytes in response to physical exercise. Activation of specific receptors enhances phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTor)/ glycogen synthase kinase 3 beta (GSK-3 β) signaling which leads to proliferation, physiological hypertrophy, and cardiac repair mechanisms in response to injury. The PI3K/Akt activation enhances endothelial nitric oxide synthase (eNOS) and subsequently intracellular nitric oxide (NO) levels, which increases contractility and decreases fibrosis as well as pathological hypertrophy. Changes in miR mediate apoptosis and influence cardiac compliance and fibrosis via alterations in collagen production and matrix metalloproteinase (MMP) expression. Sports induces mitochondrial renewal. Paracrine secretion of extracellular vesicles (Evs) containing miR or other molecules mediate/reduce I/R injury as well cellular apoptosis.

Figure 6. Molecular mechanisms in exercise-induced protection against cardiotoxicity of anthracycline.

Figure 1

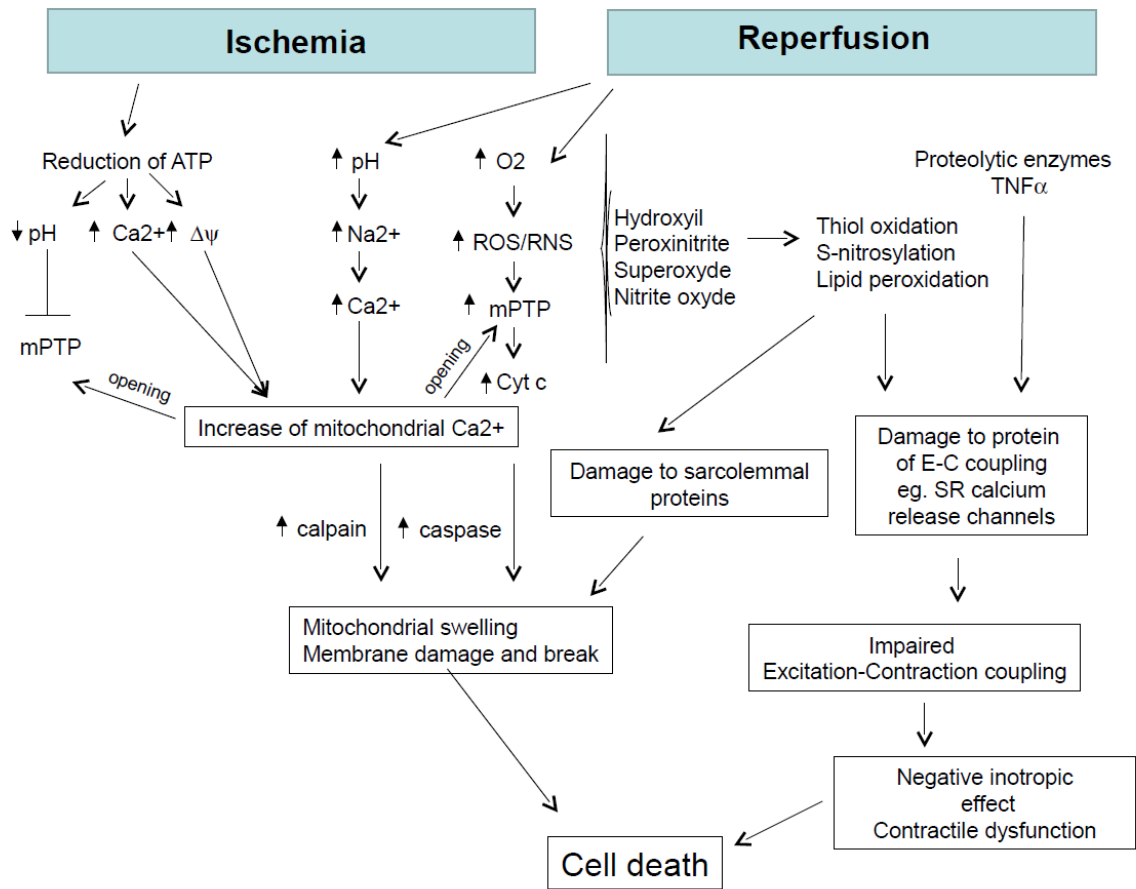


Figure 2

Ischemia/Reperfusion



Ischemic Preconditioning

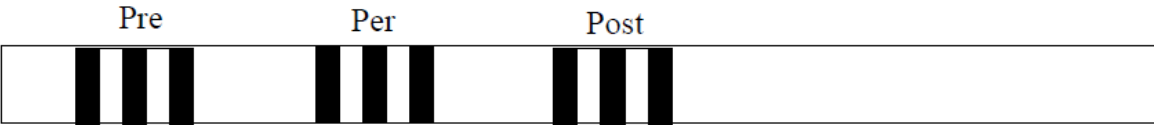


Ischemic Postconditioning



Remote Conditioning

Remote organ



Heart



Figure 3

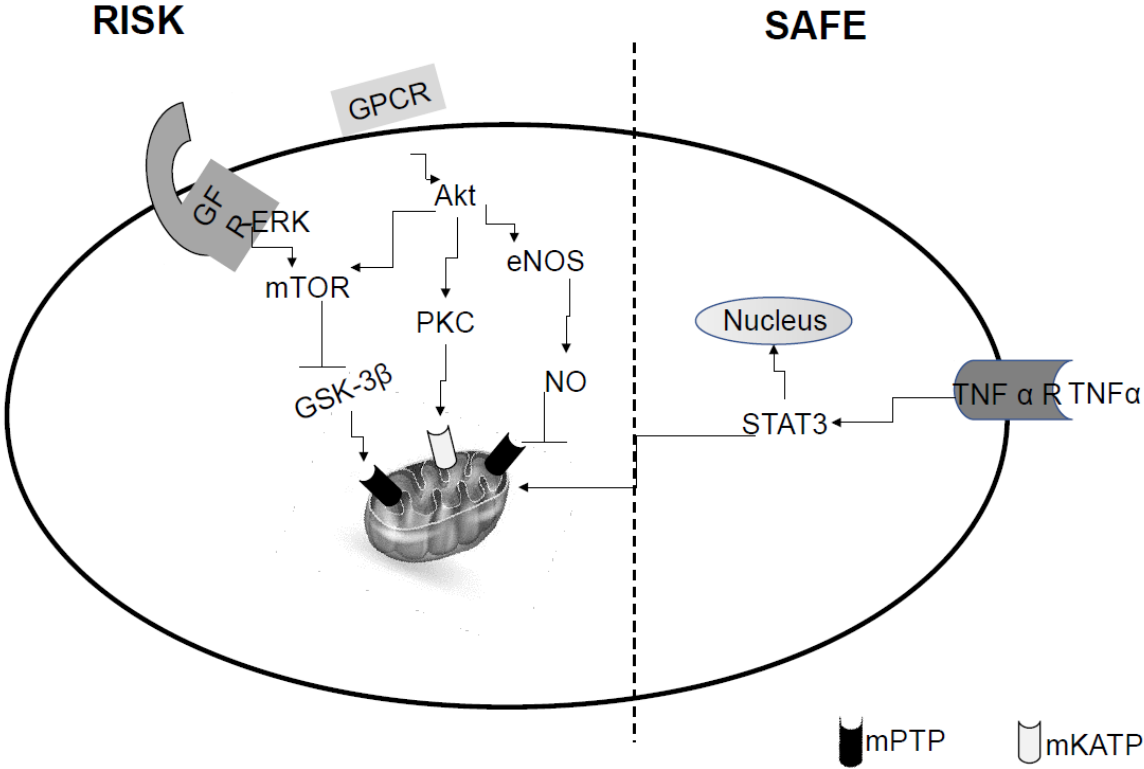


Figure 4

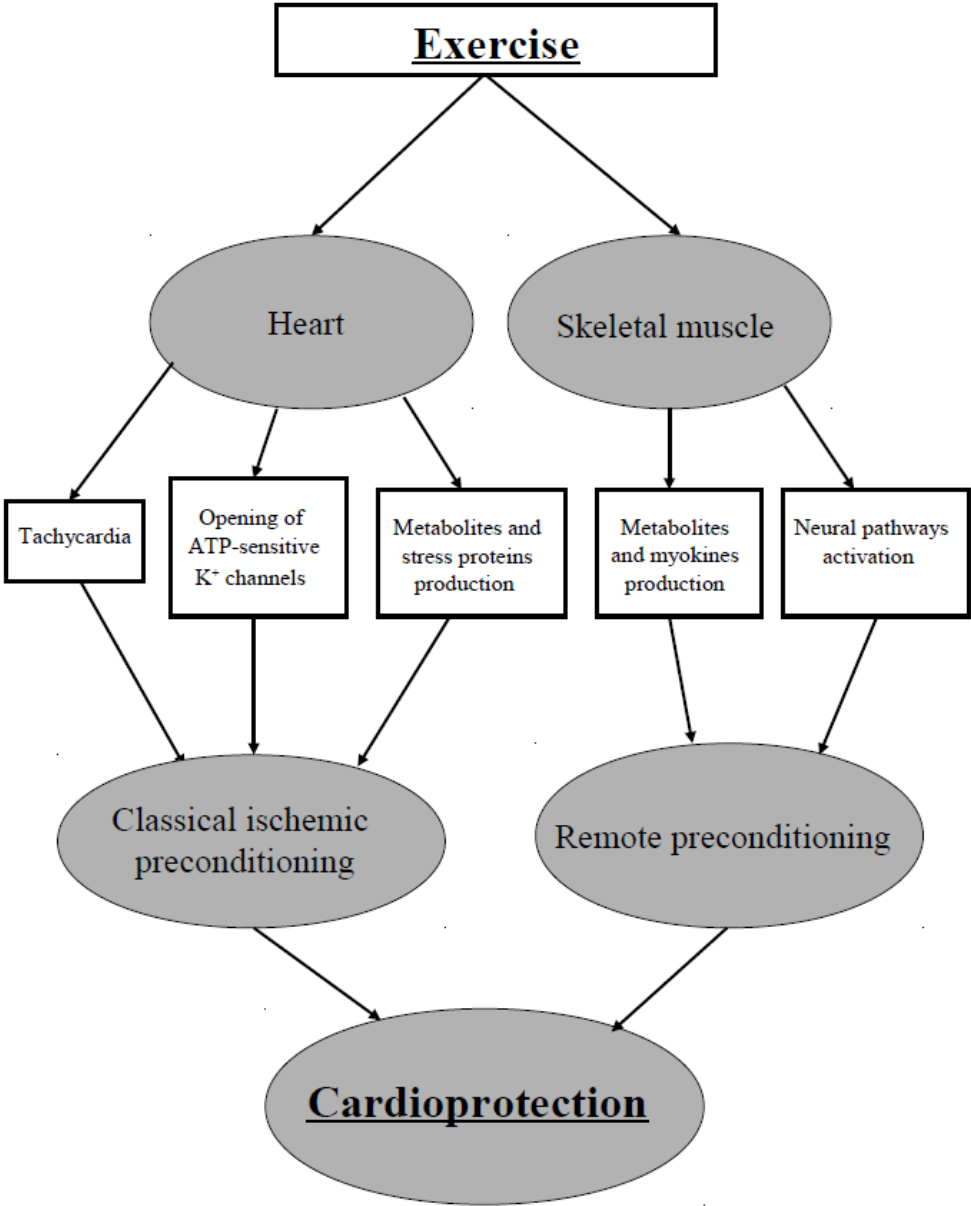


Figure 5

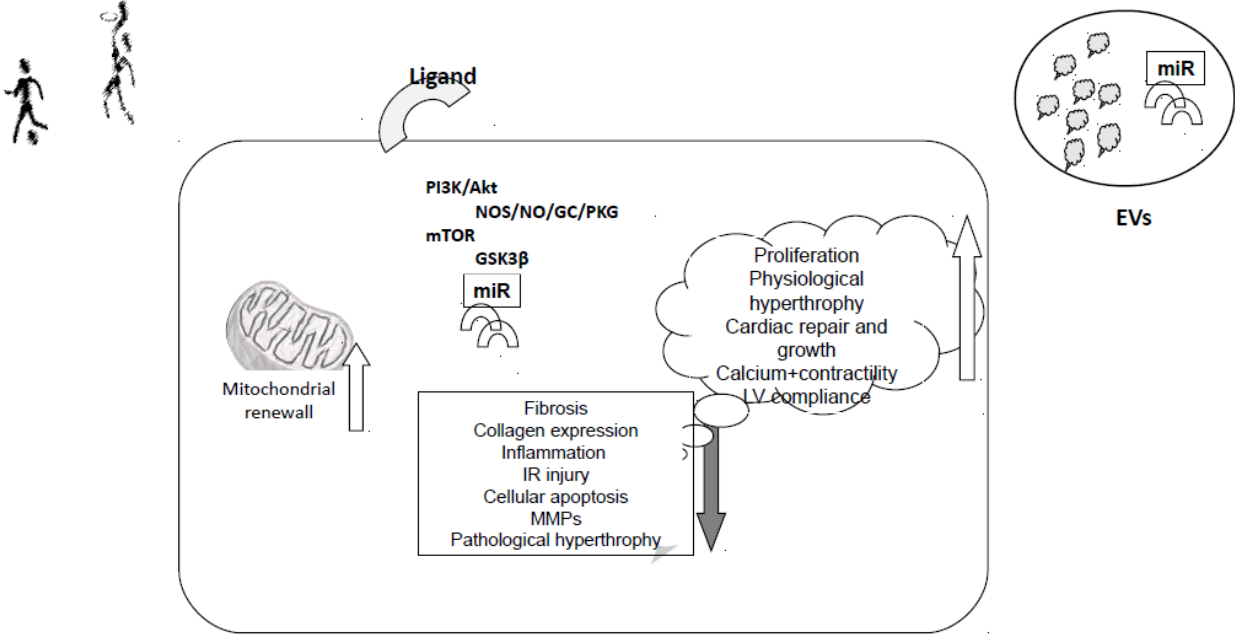


Figure 6

