Role of exercise training on pulmonary ischemia/ reperfusion and inflammatory response

Papel do exercício físico na isquemia/reperfusão pulmonar e resposta inflamatória

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Abstract

Advances in new technologies associated with improvement of knowledge in medicine have promoted important development in therapeutic and preventive approaches in an attempt to diminish complications following cardiothoracic process involving ischemia/ reperfusion (IR). Nevertheless, postoperative pulmonary injuries remain high and are considered one of the most frequent complications after cardiothoracic surgery. Thus, new strategies with prophylactic actions are crucial in the cardiovascular area in an attempt to reduce complications and to improve patients life. It is well documented that moderate exercise training is a non-pharmacological tool to prevent and/or treat the cardiovascular and endocrine-metabolic diseases. The aim of this review was to provide an update of several studies on pulmonary IR process and its local and systemic complications and the role of inflammatory response. Furthermore, this review focused on the effects of exercise training on the pulmonary IR as an important strategy to diminish its complications. This review shows that few studies exist regarding the health-promoting physical exercise in cardiothoracic surgery and how important and necessary it is to increase studies in this area. Recently, studies from our laboratory showed beneficial effects of exercise training in experimental model of pulmonary IR. Collectively, data show that physical preconditioning for patients is a very important approach to reduce postsurgical complications as well as diminish the time of hospitalization which includes a specialized personal trainer in the health team. Moreover, this preventive strategy might improve patient recovery and would lead to consuming less resources of the health care system. This review included experimental studies in English and Portuguese found in SciELO and MEDLINE (from 1987 to 2008) and also classical texts related to the topic.

Descriptors: Ischemia. Reperfusion. Inflammation mediators. Exercise.

Resumo

O avanço tecnológico associado aos novos conhecimentos científicos tem proporcionado melhora na prevenção e/ou tratamento das complicações cardiorrespiratórias advindas de cirurgias cardiotorácicas e procedimentos envolvendo isquemia/reperfusão (IR), mas os riscos destes procedimentos ainda permanecem altos. Assim, medidas profiláticas que possam reduzir o aparecimento das complicações pós-cirúrgicas em pacientes devem ser investigadas. O exercício físico aeróbio de moderada intensidade tem sido recomendado como terapia não farmacológica tanto na prevenção como no tratamento de diversas doenças cardiovasculares e endócrino-metabólicas. Assim, o objetivo desse trabalho foi realizar uma revisão de literatura sobre os mecanismos pelos quais o processo de IR pulmonar promove lesão local e sistêmica de órgãos, e o

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papel dos mediadores inflamatórios na IR pulmonar. Além disso, essa revisão abordará a influência do exercício físico moderado como abordagem profilática nas complicações advindas da IR pulmonar. Essa revisão evidencia a escassez de trabalhos na área e a necessidade de maiores estudos enfocando o preparo físico dos pacientes a serem submetidos à cirurgia cardiotorácica. Trabalhos pioneiros foram desenvolvidos em modelos animais, demonstrando a importância do exercício físico na redução da resposta inflamatória induzida pelo procedimento de IR pulmonar. Conclui-se que o preparo pré-cirúrgico dos pacientes deve envolver equipe multidisciplinar da área de saúde, com inclusão de profissional de educação física, para que a prescrição do exercício físico seja individualizada e supervisionada. Além disso, esse preparo pré-cirúrgico poderá propiciar redução das complicações advindas do processo operatório, redução do período de internação hospitalar e, consequentemente, melhora na recuperação do paciente, acarretando ainda menores gastos para o sistema de saúde. Foram utilizadas como referências publicações em inglês e português de artigos científicos nas bases de dados SciELO e MEDLINE (de 1987 até 2008) e também textos clássicos relacionados ao tema.

Descritores: Isquemia. Reperfusão. Mediadores da inflamação. Exercício.

INTRODUCTION

Pulmonary ischemia/reperfusion (IR) presents intense inflammatory response, with the infiltration of neutrophils in the lungs, endothelial injure of the micro-vases and pulmonary edema. Furthermore, IR results in excessive production of reactive species of oxygen and decrease in production or availability of nitric oxide, causing harmful effects to tissues. Moderate exercise training promotes benefic effects either in the prevention as in the treatment of several diseases, such as high blood pressure, diabetes mellitus and atherosclerosis. Despite the role of exercise as prevention against inflammatory diseases, and more specifically, against pulmonary diseases related to the process of IR, it still requires more studies. Recent researches in our laboratories using experimental models of pulmonary IR showed that moderate physical preconditioning, promotes significant beneficial effects [1-3]. Therefore, physical preconditioning can be of great relevance either to reduce comorbidities or to prevent postsurgical complications associated to the process of pulmonary IR.

This review was based on a bibliographic research of scientific articles in English and Portuguese found in the SciELO and MEDLINE database (from 1987 to 2008) and also classical texts related to the topic. The primary search strategy involved the combination of the following keywords: ischemia, reperfusion, pulmonary ischemia/reperfusion, inflammatory response, reactive species of oxygen, oxidative stress, antioxidant defense and physical conditioning. In addition, it was performed a secondary search including the list of references of the articles found in the primary search.

ISCHEMIA/REPERFUSION AND PULMONARY COMPLICATIONS

One of the situations that causes major complications after cardiothoracic surgeries is the IR process that causes intense inflammatory response, causing serious complications and pulmonary dysfunction. The reperfusion acute lesion has become an important factor of morbidity in cardiothoracic surgeries, with significant impacts in expenses and health care. Furthermore, the International Heart and Lung Transplantation Society showed that the most significant risk factors for the development of postsurgical complications or death for transplanted patients are: donor's age and time of organ's ischemia [4]. Although there are considerable advances in the transplantation immunology area, the reperfusion acute lesion or the reimplantation response remain as considerable source of morbidity, reckoning, diagnostic and the management of postsurgical complications still need further advances [5].

The integrity of the endothelial cells and the vascular smooth muscles is of crucial importance in the maintenance of alveolar perfusion for the pulmonary physiology, regarding gas exchange and homeostasis of the system. The blood vessels, usually, have three layers: the inner layer, which is in contact with the blood elements and basically consists of endothelial cells; the middle layer, consisted by smooth muscle cells; and the adventitial layer, consisted by fibrous conjunctive tissue which overlays the external part of the vessel. The endothelial cells are responsible for the synthesis, metabolism and release of a large variety of mediating agents that regulate the vascular tonus, vascular permeability, metabolism of endogenous

and exogenous substances, and platelet and leukocyte activity. The substances produced by the endothelium can be divided in vasodilating agents, such as prostacicline (PGI_2), nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF), and vasoconstrictor agents, such as endothelines, prostaglandin H_2 (PGH_2), tromboxane A_2 (TXA_2) and the reactive species of oxygen (RSOs) [6]. Amongst this variety of substances, the NO deserves special attention due to its role in the mechanism of vasodilation and neutralizer of EROS. Enzymes known as NO synthesis (NOS), which are divided in two large groups of constitutive isoforms (cNOS: eNOS-endothelial and nNOS-neuronal), and undividable isoform (iNOS) are capable of catalyzing the oxidation of terminal nitrogen of the guanidine group of L-arginin, forming NO and L-citrulin. Once released, NO promotes several actions in the cardiovascular system, among them, platelet aggregation inhibition, vasodilation, inhibition of cellular growth and inflammatory response and neutralization of RSOS [7]. In addition, the endothelial cells present in the lung vessels play important role in the synthesis and degradation of substances present in the blood, such as angiotensin and bradicinin [6].

Vascular functional alterations associated to the process of IR may be involved in pulmonary complications related to the development of several diseases, such as pulmonary high blood pressure (PHBP) and acute respiratory anguish syndrome (ARAS). The PHBP is defined as an increase in the mean pressure of the pulmonary artery higher than 25 mmHg (rest) or higher than 30 mmHg (exercise), with occlusion pressure of the pulmonary artery lower than 15 mmHg [8] and it is considered a serious clinical situation. It is known that the lesion and/or dysfunction of the endothelial cells is related to the development of PHBP, to the unbalance between the vasodilating and vasoconstrictors mediators, including the decrease in production of PGI_2 and NO and increase in the production of endotheline (ET-1) and TXA_2 [9]. The initial endothelial lesion results in restoring local vasoactive mediators, promoting a pro-clotting state, leading to the consequent vascular obstruction. Moreover, defects in the potassium channels of the smooth muscles of the pulmonary circulation seem to be involved in the beginning and/or progression of PHBP [10].

The acute respiratory anguish syndrome (ARAS) is considered the most serious respiratory dysfunction [5,11]. ARAS is described as an event of acute pulmonary lesion, associated to an acute pulmonary edema, non-hydrostatic or non-cardiogenic, followed by a serious hypoxemia, responsible for high rates of mortality. It is characterized by damage to the endothelium and pulmonary epithelium, with consequent lesion to the capillary alveolus membrane. There are many mediators that are ascribed as cause and

perpetuators of the syndrome, but, in general, its pathogenesis consists of two aspects: the direct effects of the lesion on the pulmonary cells and an acute systemic inflammatory response that may include cellular and humoral components. Despite the fact of ARAS having been first described more than 30 years ago, many doubts still persist regarding its definition, physiology, physiopathology and treatment [12-14].

The IR pulmonary lesion consists in an important common physiopathologic event to several situations in clinical practice. Its local and systemic effects can be studied in conditions that involve lung transplantation, cardiothoracic surgery, occlusion of the pulmonary artery, pulmonary thromboembolism, total pneumothorax and important pleural suffusion [15]. Ischemia is characterized by the interruption of oxygen and nutrients supply to a certain area, it leads to tissue dysfunction and, depending on the degree of ischemia, it can cause necrosis of the tissues. The damages to the tissues depend on the characteristics of the tissue involved, ability of capillary restoration in microcirculation, metabolic demand, available oxygen supply, and the ability of producing energy by anaerobic metabolism. The IR lesion can be defined as the damage that occurs in a tissue with the restoration of blood flow, after the period of ischemia [16-18].

Evidences show that the lesion of tissues is not only limited to ischemia, but during or after reperfusion, tissue compromising is also of great clinical relevance. Reperfusion can damage individually an organ severed by ischemia, as it occurs in organ transplantations or it can extent to other organs, due to a systemic inflammatory response, in which inflammatory mediators are produced and released in the blood flow, reaching deferent organs [19-21].

The pulmonary ischemia occurred as result of the pulmonary artery occlusion followed by reperfusion is associated to the infiltration of neutrophils in the lungs, endothelial lesion of the microvases and pulmonary edema [22,23]. The RSOs derived from the neutrophils can cause tissue and vessel damage by the adherence of polimorfonuclear neutrophils in the endothelial cells [20,24]. Furthermore, the cellular response involves neutrophils, macrophages/monocytes and lymphocytes, which have an important role in the process that includes bonding, chemotaxis and the activation of these leukocytes [14,16]. This intercellular interaction is done by bonding molecules (adesines, integrines and selectines), present in the endothelial cells and inflammatory [25]. The events involved in the systemic inflammatory response include plasmatic alterations, such as activation of the complementary system, coagulation/fibrinolysis and cynines, increase of the pro-inflammatory mediators; cytokines as a factor of tumoral necrosis α (TNF-α), interleukin 1β (IL-1β), interleukin 6 (IL-

6), interleukin 8 (IL-8), oxidant lipid mediators, proteases, nitric oxide and neuropeptide and induction of protein synthesis. These factors are considered responsible for cellular damage and alterations in the surface-active agent (an important substance that acts reducing the superficial tension of the liquids that overlay the interior of the alveoli and other respiratory means), disturbing the ventilation/ perfusion relation, resulting in hypoxemia [26]. Commonly, the IR corresponds to the anoxia-reoxygenation in the transplanted organs, however, the lungs are considered different, for they contain oxygen in the alveoli during ischemia. Thus, in the lungs, the oxidative stress resulting from ischemia must be distinguished from that resulting from other organs [18,27,28].

INFLAMMATORY RESPONSE IN THE ISCHEMIA/REPERFUSION PROCESS

The cytokines consist of a large number of glycoproteins of low molecular weight that act in the cellular intercommunication. The most important aspects of these proteins are their vast specter and action potential. They can be produced by any cell of the body, but the erythrocytes and they are related to stimulation and suppression of the events of immune response, triggering and coordinating the inflammatory response [29].

The inflammatory response that can lead to dysfunction and failure of an organ is one of the most serious problems after the occurrence of lesions under different conditions, such as in sepses, serious burning, acute pancreatitis, hemorrhagic shock, trauma and transplants [30,31]. It is known that pro-inflammatory cytokines have an important role in the IR lesion of the heart, kidneys, small intestine, skin and liver, but little is known about their role in pulmonary IR lesion [32].

An important cytokine is released during the IR process is TNF-α. This cytokine, besides of having a direct cytotoxic effect on the endothelium, stimulates the production of other cytokines, such as the interleukins. These substances interact with the endothelial cells, increasing the pro-coagulating activity and the production of the plasminogen inhibitor, facilitating coagulation and promoting the activation of neutrophils, monocytes and lymphocytes that on their turn, release superoxide anions (O_2^-) and other RSOs that participate in the process of endothelial tissue lesion [31]. Studies evidence that the TNF-α alters the selectivity of the endothelial barrier and produces pulmonary edema in experimental models, the TNF-α increases the pulmonary vascular resistance, which results in alveolar edema, being a result of the release of tromboxane A_2 (TXA_2) in response to the activation of polimorfonuclear leucocytes [33,34].

Another important interleucine in the inflammatory response linked to the IR is IL-1β, characterized also as pro-inflammatory, is connected to the activation of neutrophils and induces the connection of molecules linked to the leucocytes and endothelium. The IL-1β induces the action of the cicloxigenase (COX) and the expression of the inductive nitric oxide syntax (iNOS). It also increases the expression of other cytokines such as the TNF-α, IL-6 and the linking molecules [35]. The COX is an important enzyme present in the cellular membranes, that produces prostanoids from the arachnoidal acid, it can be divided into two subtypes, COX-1 and COX-2; more specifically, the COX-2 is associated to the inflammatory response and production of important mediators, such as the cytokines [36].

The IL-6 possesses an important role in the acute inflammatory response and it is produced by different types of cells, such as monocytes, fibroblasts and endothelial cells, being the main source for the production of the IL-6, lipopolysaccharides, IL-1 and TNF-α. Initially, it was believed that the IL-6 played only a pro-inflammatory role, but recent studies suggest that it plays an anti-inflammatory role as well, being very important for the return of homeostasis after the inflammatory process. High plasmatic concentrations of IL-6 have been confirmed in several conditions in which the homeostasis of the system is compromised or jeopardized such as sepsis or multiple traumas [37,38]. The role of the IL-6 in the lung transplantation is still not well established and there are conflicting results. Although, high levels of IL-6 were observed in the lesion of respiratory means and pulmonary tissue after inflammatory stimuli, but the functional relevance of these findings still remains unclear[39,40].

OXIDATIVE STRESS AND REACTIVE SPECIES OF OXYGEN

Several authors have shown direct association between the increase in the production of reactive species of oxygen (RSOs) and several human pathologies, among them brain stroke, myocardial infarction , atherosclerosis, IR lesion, rheumatoid arthritis and aging [41-43]. Furthermore, the RSOs play an important role in ARAS and in pulmonary and vascular lesion after the process of pulmonary IR [44]. Especially, the neutrophils linked to the pulmonary vascular endothelium during pulmonary IR are responsible for the tissue damage through the production of the RSOs [26,45].

The oxidative stress involves the production of RSOs by different cells of the body, such as the endothelial cells, the smooth muscle cell, cells from the adventitial layer, cells from the immunologic system, among others. The RSOs are formed by intracellular and extracellular enzymatic activity, being the oxidase xantine, the cytochrome P450, by the cycloxigenase, the endothelial nitric oxide sintetase

(eNOS) disconnected and the NADPH oxidase, the main enzymes involved in this process. The NADPH oxidase is the main forming enzyme of superoxide anion (O_2^-) that possesses high cytotoxicity and is involved in the genesis of the pulmonary IR lesion [46-48].

The NADPH oxidase is an enzyme consisted of several subunits, such as the p22[phox] and gp91[phox] (Nox2), p47[phox], p67[phox], p40[phox], and the small guanosine-triphosphate (GTP)-linked to the Rac protein [48,49]. This complex is involved in the production of O_2^-. The enzyme eNOS disconnected may also be an important source of O_2^- and the aforementioned production occurs when the bioavailability of L-arginine or of (6R)-5,6,7,8-tetraidrobiopterine (BH_4), substrates for the formation of nitric oxide (NO), are in short concentrations [50]. The reaction of the O_2^- with the NO produced by the endothelial cell reduces its bioavailability, generating a highly unstable molecule, the peroxinitrite ($OONO^-$), capable of oxidizing proteins, lipids and nucleic acids, causing cellular damage through the activation of the nuclear factor kappa B (NF-kB), growth factors, and cytokines, that on their turn trigger structural and functional alterations, such as the vascular remodeling, increase of extracellular matrix proteins deposition, increase in the inflammatory process and endothelial permeability in the tissues involved [51].

The antioxidant enzymes consist in the main line of defense to the oxidant components of the system. Amongst the antioxidant enzymes present in the vascular tissue, there is the catalase (CAT), glutatione peroxidade (GSH-Px) and more three types of superoxide dismutase (SOD), being the SOD-1 dependent of the Cu/Zn, present in the nucleus and in the citosol, the SOD-2 dependent of the Mn, present in the mitochondria and the SOD-3 dependent of the Cu/Zn, present in the extracellular matrix. In the SOD enzyme, its system seems to be specific for the dismutation of O_2^-, thus, forming hydrogen peroxide (H_2O_2). The CAT and the GSH-Px play an important role in the elimination of H_2O_2, thus, promoting water formation. The perfect balance among the antioxidant enzymes is important for maintaining cellular integrity, for SOD, CAT and GSH-Px prevent the accumulation of O_2^- and H_2O_2, preventing cellular damage [52] (Figure 1).

EXERCISE TRAINING AND BENEFITS FOR PREVENTING DISEASES

Exercise training is an activity performed with a systematic repetition of oriented movements, with consequent increase in the consumption of oxygen due to muscular requirement. Exercise training provokes a series of physiological responses in the body systems and, especially, in the cardiovascular system, aiming to maintain the cellular balance due to the increase of metabolic demands and consumption of energy [53,54]. It is known that moderate exercise training, performed on a regular basis, promotes positive effects either in preventing as in the treatment of cardiovascular diseases, and its regular practice has been recommended by different health associations throughout the world. Its benefits have also been shown in the prevention and treatment of high blood pressure, diabetes mellitus, dislipidemia, obesity and osteoporosis. Thus, the low levels of physical activity or exercise training are considered risk factors for the development of these diseases [55-57].
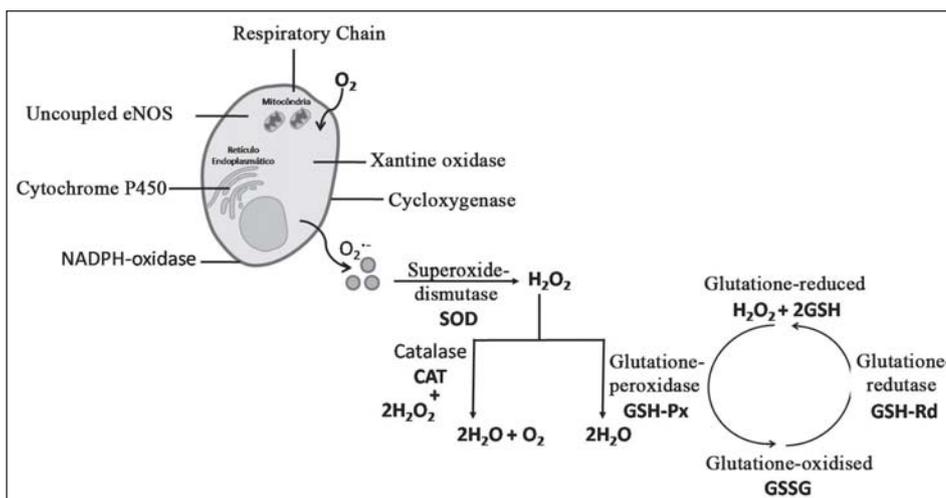

Fig. 1 - Oxidant and antioxidant enzymatic system. eNOS = endothelial nitric oxide synthesis; $O_2^{\cdot-}$ = super-oxide anion; H_2O_2 = hydrogen peroxide). Adapted from Fortuño et al. [48] and Ray & Shah [49]

These benefits are related to the increase in production of vasoactive substances, such as NO, and/or to the increase of its availability in the endothelial cells [58-60]. It is known that exercise training increases the flow of pulsating blood and the pressure that the blood exerts over the vascular wall and the shearing force over the endothelial cells are powerful stimuli for generating NO in the vascular system. Therefore, one of the beneficial effects of regular exercise training is closely related to its ability of stimulating the synthesis of NO by the endothelial cells [61,62]. Another vascular change caused by exercise training is related to the expression and activity of antioxidant enzymes. Amongst these enzymes, the SOD-1 Cu/Zn is the most sensitive to the shearing force caused by exercise training [63].

Nevertheless, there are few studies relating the chronic role of exercise training as protector against inflammatory diseases, and more specifically against pulmonary diseases associated to the pulmonary IR lesion. The response of cytokines to acute exercise differs from that seen in the IR lesion IR. It is noticed that classical pro-inflammatory cytokines, TNF-α and IL-1β, generally do not increase with exercise training, indicating that the cascade of cytokines induced by exercise training differs from the cascade induced by the IR [64,65]. Recent studies performed in our laboratory using experimental models showed that moderate physical training previous to the process of IR

pulmonary IR promotes a decrease in the overfilling of proteins in the lungs, diminishing vascular permeability and, consequently, pulmonary edema permeability. Physical training also promoted decrease in the plasmatic levels of the TNF-α and IL-1β, increase in the plasmatic activity of the antioxidant enzyme SOD in this experimental model [2]. More recently, it could be observed that physical training promotes reduction in the super-expression of the cytosolic subunit of the NADPH oxidase p47^{phox} triggered by pulmonary IR in the mesenteric artery of rats [3]. All these data evidence the beneficial effects of physical training in preventing inflammatory responses before the process of pulmonary IR, as well as increase in the antioxidant defense, crucial for the control of RSOs. It was also shown that pulmonary IR causes local and systemic vascular and inflammatory alterations in the body, and physical training helped controlling these alterations on a systemic level [1-3] (Figure 2).

The protocol of exercise training known for improving cardio-respiratory ability is the moderate type (running, swimming, bicycle-riding are the most common), with intensity between 50 to 75% of maximum oxygen consumption (VO$_2$max), with 3 to 5 weekly sessions and duration between 30 and 60 minutes of continual activity [66,67]. Considering the great individual variability in response to exercise training prescription regarding the amount of training (involving intensity, frequency and
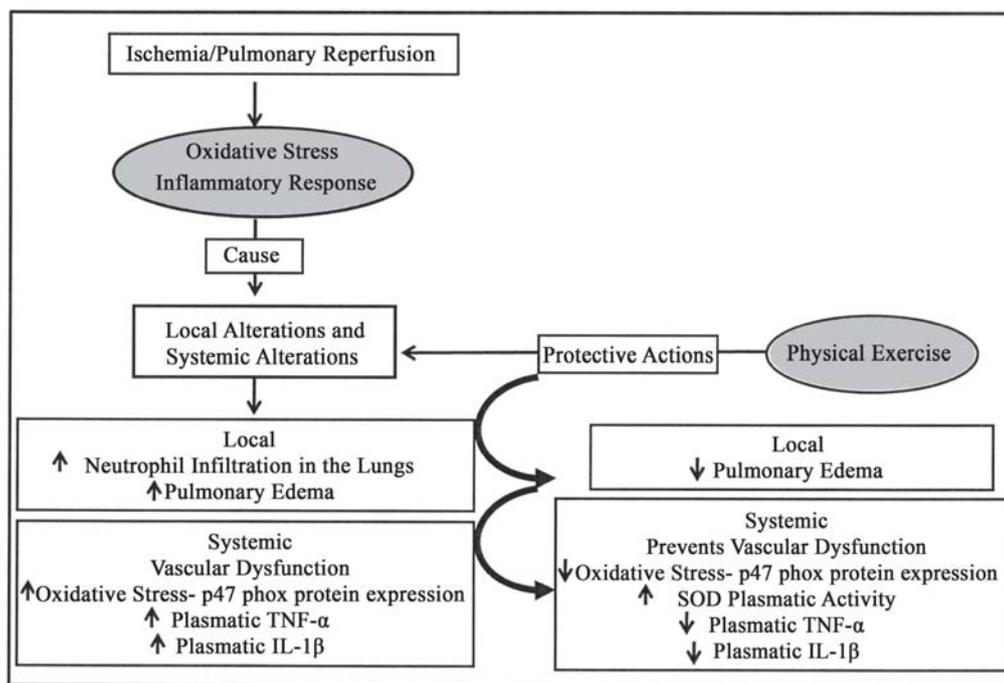

Fig. 2 - Effects of moderate exercise training previous to the process of pulmonary IR. TNF-α = tumoral necrosis factor α ; IL-1β = interleukine 1β; SOD = super-oxide dismutase;, p47phox = cytolosic sub-unit of NADPH oxidase p47phox

duration) it is necessary to evaluate the physical and clinical conditions of each individual in order to attain the most beneficial effects.

Thus, the intensity of exercise training can be measured by the maximum cardiac frequency (maxCF) using the formula: maxCF = 220 – age. From that formula is possible calculate the desired maxCF rate, and then determine the different intensities, considering moderate exercise between 55 and 80% of maxCF. It is also possible to determine the intensity of exercise training from the reserve cardiac frequency (reserveCF), in which is considered the cardiac frequency at rest (restCF) and it is applied the following equation [68]: reserveCF = CF rest + I. (maxCF – CFrest); where I is considered the intensity of exercise to be performed in decimal, moderate between 50 to 75% of the CFreserve. The Borg scale of subjective perception of effort must be also used in the training follow-up, considering as reference a moderate level from 12 to 14 in the scale [69,70].

Specifically, the physical exercise program in preparation of patients for cardiothoracic surgeries must involve exercise training (gym bicycle or running on a treadmill) 3 to 5 times a week, from 10 to 30 minutes, that must be done at the same intensity (continuous), between 40 to 60% of the CFreserve, during a period of at least 8 weeks previous to the surgery. Many patients presented limitations due to the decrease in respiratory functions, the moderate exercises produce the best results and must be encouraged; however, the low intensity exercises are also benefic for those patients that are unable to reach that intensity. Breaks during the training can be useful and efficient in promoting tolerance in the practice of exercises of low and moderate intensity. The exercise prescription must involve careful clinical evaluation, making sure that the training sessions as well as the prescription of exercise training must be done by a physical education professional, and be under his supervision. Therefore, the preoperative preparation of patients must involve a multidiscipline health crew. Furthermore, the inclusion of exercise training as a preoperative preparation might be able to reduce the complications resulting from cardiothoracic surgery, reduce the period of hospital internment and, consequently, improve the patient's recovery, which will cause the Health System expenses to be cut down.

The benefits of regular practice of exercise training have also been shown in pulmonary rehabilitation, with increase in the pulmonary function and quality of life in individuals submitted to pulmonary transplantation. These studies involved exercise training (gym bicycle and walking on a treadmill), 3 to 5 times a week, for 30 to 60 minutes, intensity 30 to 60% CFreserve and subjective perception of effort 13 to 14. The minimum time after the transplantation to start the training protocol in these studies varied between 1 and 6 months [71-73]. Thus, the physical training must also be done after the surgery in order to improving the quality of life of the patient and providing independence in his daily and professional activities.

CONCLUSION

The process of pulmonary IR is associated to the infiltration of neutrophils in the lungs, pulmonary edema, intense inflammatory response and local and systemic vascular alterations with a high rate of morbidity and mortality. Moderate exercise training has been employed as an important tool in preventing and/or treating several cardiovascular and endocrine-metabolic diseases. Studies in healthy animal models showed that the regular practice of previous physical exercise improves and/or prevents local and systemic lesions caused by the process of pulmonary IR. Therefore, the regular practice of supervised physical exercise would be of great relevance either in reducing co-morbidities or in preventing postoperative complications associated to the process of pulmonary IR. Consequently, the inclusion of low and moderate exercise training as preoperative preparation and as auxiliary in the postoperative recovery process is of great relevance in the cardiovascular surgery area, for it will result in reduction of the complications caused by the surgical procedure, reduction of the hospital internment period and, consequently, improve in the patient's recovery, resulting in a significant reduction in the costs for the Health System.

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