Effect of physical training as positive modulator on the alterations in the neuro-immune-endocrine axis in patients with chronic heart failure: possible role of the tumoral necrosis factor-α

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ABSTRACT

Chronic physical exercise or physical training (PT) has been widely used in the last years with therapeutic and preventive purposes in a series of pathophysiological conditions, including cardiovascular disease. Besides the cardiovascular benefits, PT seems capable to modulate in pathophysiological conditions, at the presence of an abnormal inflammatory response, including over expression of proinflammatory cytokines through a neuro-immune-endocrine interaction. Nowadays chronic heart failure (CHF) is reviewed as the consequence of an interplay of hemodynamic, neurohormonal, immunological and endocrine mechanisms. This abnormal inflammatory response, including the over expression of proinflammatory cytokines may be proposed as responsible for the progression and clinical deterioration in CHF. Tumor necrosis factor-α (TNF-α) is the main proinflammatory cytokines involved in the inflammatory cascade implicated in the pathophysiological of CHF. PT may improve exercise performance by modifying the inflammatory status, as well as by allowing reversing the inflammation-induced harmful effects on the cardiovascular system, and that PT may represent an important immunomodulatory option that may be possible to intervene in the progression of the disease.

INTRODUCTION

Chronic physical exercise or physical training (PT) has been widely used in the last years with therapeutic and preventive purposes in a series of pathophysiological conditions, including cardiovascular disease¹⁻⁴, among others. The potential beneficial effects of physical exercise chronically performed in several distinct situations, in other words, in pathological conditions or with the objective of improving the athletic performance seem to be associated with the fact that physical exercises promote adaptations in all compartments of the animal body⁵. These alterations may be characterized as an organic and functional reorganization in function of inside and outside requirements. The persistent alterations on the structure or function are particularly associated to responses to the stimulus generated by physical exercises systematically performed along time⁶.

The physical training program is composed of: constant-overload repetitive phases, phases with increases on the overload (overreaching), phases of maintenance of this increase (overtraining) and recovery phases⁷. The overload phases are characterized by the difference between the total amount of overload (volume x intensity x density) and the recovery time between training sessions. Thus, the recovery phase between training sessions is necessary and enables the restoration and the improvement on the exercise performance, metabolism and homeostasis along time. When the recovery time is sufficient, this situation is characterized as overreaching. On the other hand, if the recovery time is not sufficient and it lasts for a long period, a state of chronic alterations (molecular, biochemical and regulatory) may be obtained, leading to disorders that involve well-being, increases on the incidence of diseases and impaired performance during exercise. The balance between the training specificity, physiological stressors and others and the recovery process determine the results or the positive adaptations of a given period of physical training⁸⁻¹⁰.

Thus, Lehmann et al.⁹ proposed a biphasic model of the training overload response predominantly involving: 1 - peripheral mechanisms at initial overload phases and 2 - central mechanisms at more intense overload phases or overtraining. This means that muscular lesions and the metabolic demand are mainly involved in the acute response to training and the chronic alterations lead not only to alterations on the tissue metabolism, somatic differentiation, body composition and functionality of organs, but also to central regulatory dysfunctions¹⁰.

The hypothalamus plays a central integrating role of all afferent signalization to the brain and also an important role in the regulation to the central responses to stress and physical training⁹. These interactions include afferent information from the autonomous nervous system, direct metabolic effects, hormones and cytokines, as well as information from upper cerebral centers, demonstrating a complex interaction involving the bidirectional communication between neuroendocrine and immune systems⁴⁻¹⁰.

Physical training and the immune system

During the last twenty years, many efforts have been made in order to understand the mechanisms responsible for the interaction between physical exercise and the immune system and to study the effects of the physical training on health⁵,¹⁴⁻¹⁷.

Currently, the fact that the physical training improves physical capacities such as motor strength, aerobic resistance, among others is well established, thus contributing for a better physical and psychological condition¹⁸. Epidemiological evidences have demonstrated a positive correlation between the practice of physical activity and the decrease on the mortality rate incidence of several types of cancers and other chronic diseases¹⁵,¹⁸,¹⁹⁻²¹.

According to Pedersen & Hoffman-Goetz¹⁹, the increasing number of studies on physical exercise and immune system has demonstrated an important modulating effect of the function of cells

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from the immune system possibly on the system as a whole. These effects are regulated by several factors including the exercise-induced release of proinflammatory cytokines, hormones and hemodynamic effects that lead to a cells redistribution. The nature of this interaction is complex and not fully understood. Some alterations observed are: modifications on the expression of adhesion molecules, selective recruitment of mature lymphocytes and impairment of the mitosis and apoptosis processes in the immune system cells.

These alterations, however, have raised the interest of using the chronic physical exercise or the physical training performed at moderate intensities (<60% VO\textsubscript{2max}) as alternative non-pharmacological therapeutics in some pathological situations\cite{15,16}, where at this intensity, epidemiological evidences demonstrate higher infections resistance on the upper respiratory tract\cite{22,23}.

Some hypotheses have been proposed in order to explain the relation between the regular practice of physical exercise and the susceptibility of acquiring infections both among athletes and among inactive individuals. Nieman\cite{24} proposed a "J" shape curve model that describes a relation between the amount of exercise and the incidence of infections on the upper respiratory tract. Pedersen & Ullum\cite{25} proposed the "open window" model, period in which after intense (> 75% VO\textsubscript{2max}) and long-duration (> 1 hour) exercise, a high risk of infection due to the post-exercise immunosuppression is observed.

The relevant point of both hypotheses is that both suggest that moderate intensity exercises present an stimulating effect on the immune function, also presenting practical implications when applied conjointly to pathological situations such as cancer\cite{26}, in infectious conditions such as poliomyelitis, myocardial diseases, HIV and aging\cite{15,17,21}.

In this context, two research lines have been currently proposed in the attempt of understanding the mechanisms that support these hypotheses in order to establish a connection between exercise and the immune system: a metabolic approach involving the glutamine metabolism\cite{25}, and other, that considers alterations on the neuroendocrine milieu as an immunomodulation mechanism\cite{26}.

**Alterations on the immune system in the chronic heart failure**

The acute myocardial infarction is associated with an inflammatory reaction, which is prerequisite for cicatrization processes\cite{27}.

The heart ischemia situation causes alterations on the mechanisms of defense against the formation of oxygen reactive species, as the production of free radicals is increased\cite{20}. These latter potentially wound the cardiac myocyte and the vascular cells and may be involved in the mediation of the inflammatory cascade through the induction of cytokines\cite{27}.

After these initial occurrences, the response to the myocardial infarction is associated with the coordinated activation of a series of cytokines and the activation of genes for the synthesis of adhesion molecules. On the other hand, the mechanisms responsible for the activation of the cytokines cascade have only been investigated in recent years. Initial studies conducted by Frangogiannis et al.\cite{22} indicate an important role the mast cells play in the mediation of the cytokines cascade and release. These cells are an important source of TNF-\alpha, chemokines and growth factors. The constitutive presence of TNF-\alpha in heart mast cells in canines led these authors to postulate that the mast cells-derived TNF-\alpha may be released following the myocardial ischemia, representing an important source of this cytokine in the initial phases of the inflammatory process.

Myocardial dysfunction and heart failure are expressions that correspond to the drop on the heart mechanical performance that may be slight (dysfunction) or intense (failure). In patients with moderate or relatively intense myocardial dysfunction and those with heart failure, the damage on the myocardial function may be detected by means of studies on the cardiac pump total function, where lower degrees can only be detected by more specific indexes of myocardial contractility. The dysfunction or advanced failure conditions, the cardiac pump overall function (and the cardiac debt in rest) may be maintained within normality levels through compensatory mechanisms such as the increase on the ventricular filling, the increase on the pre-load (dilation) and/or the cardiac hypertrophy. In the myocardial infarction, the heart failure primarily occurs due to the loss of cells and secondly due to the chronic hypertrophy associated to the cicatrization or to the hypertrophic dysfunction. Finally, the heart failure associated to mechanical abnormalities that may be present ends up by leading to damages on the systolic function of the pump with sufficient intensity to determine the heart pump overall failure\cite{30,31}.

Thus, the myocardial infarction chronic alterations and hence the heart failure may be considered as an event that induces to structural, hemodynamic and functional generalized alterations\cite{25,26}, and both chronic and acute forms are considered as a stress condition to the organism. On the other hand, in the last years these alterations have been considered as a progressive and chronic disorder that affects different metabolic and physiologic features. Recently, this condition has been reconsidered as an interaction between hemodynamic, neurohormonal, endocrine and immunological mechanisms that would have adaptive effects for the organism to compensate the loss of the heart capacity to pump blood adequately\cite{32}.

The comprehension of the pathophysiological aspects of the chronic myocardial infarction and hence the chronic heart failure (CHF) is a hard task especially due to two reasons: Firstly, this condition may have several causes such as heart ischemic diseases, myopathic dilated cardiomyopathy and valvular dysfunction that compose most cases. Second, the CHF is a multi-systemic disorder that affects not only the cardiovascular system but also the muscle-skeletal, renal, neuroendocrine and immune systems\cite{28,36,37}.

In past, the myocardial chronic failure pathogenesis was understood and explained through a cardiovascular model. Currently, clinical and experimental evidences demonstrate that this hypothesis is unsatisfactory to explain symptoms experienced by patients in full, as well as peripheral manifestations of the disease\cite{28,38}, suggesting that the immune and the neurohormonal systems may play an important role in this process\cite{28,37}.

According to Shan et al.\cite{39}, the CHF is a state of immune activation with proinflammatory cytokines that contributes for manifestations both of central and peripheral orders. Thus, it has been proposed that this abnormal inflammatory response, including the high expression of proinflammatory cytokines, soluble adhesion molecules and chemotactic factors may be responsible for the development and clinical deterioration in the CHF\cite{38,40}. In this context, the main cytokines involved in the pathophysiological role of the chronic heart failure are the tumor necrosis factor-alpha (TNF–\alpha) and the interleukine-6 (IL-6).

The TNF-\alpha was originally identified by its powerful cytotoxic effect against tumoral cells. It deals about a trimeric polypeptide (17 KD) mainly produced by activated monocytes and macrophages and by other cells such as lymphocytes, fibroblasts and, neutrophils, smooth muscle and mast cells\cite{38,41}. This cytokine may act in almost all types of nucleated cells through an interaction with membrane receptors or as a soluble molecule, both biologically active\cite{35,40,42}. Moreover, the heart myocyte from adult mammals is able to produce TNF-\alpha after extracellular stimuli such as endotoxins, hypoxia or the increase on the mechanical stress\cite{37}.

The TNF-\alpha acts at cells level through two types of receptors: type I (TNFRI) and type II (TNFII), and the presence of these two types of receptors in the heart myocyte of humans was recently demonstrated\cite{40}. The fragments of the extracellular domains of both TNF-\alpha receptors (types I and II) may be released from the cell membrane and detected in their soluble form (sTNFRI and sTN-
with CHF, being particularly associated with a higher severity of cardiovascular diseases(1,3). It is generally employed as a multidimensional way of reducing the risk factors that predispose individuals to cardiac and an important non-pharmacological way of treatment and alteration in the metabolic processes, minimising the risk factors that predispose individuals to cardiovascular diseases(38,40,41).

The effect of TNF-α on the cardiac function depends on the amount and duration on the gene expression of this cytokine. This increase, when acute, may have an adaptive effect on the heart for different stress forms, and when chronic, it may perform opposite effect, impairing the adaptive processes and producing cardiac discompensation, what suggests that this cytokine plays dual role(36,41).

High TNF-α concentrations have been found in some patients with CHF, being particularly associated with a higher severity of the clinical aspects in the heart failure(41,46). TNF-α may be the main cause of a series of metabolic dysfunctions present in individuals with heart failure such as: high metabolic rate(36,38), decrease on the blood flow to peripheral tissues(40) and alteration on the protein and lipid metabolism(41). Besides its known thermogenic effect, high concentrations of this cytokine may be associated with the elevation on the insulin plasma concentrations, abnormalities on the steroid hormones metabolism, growth hormones(36), dysfunction of the left ventricle(41,47) and exercise intolerance(40,47-49).

Recent studies demonstrated the presence of high TNF-α concentrations in individuals with cardiac cachexia, and this cytokine is an important weight loss predictor(57).

However, in relation to the mechanisms responsible for inducing this increase on the TNF-α production, not much is known and thus, some hypotheses have been proposed. It is well known that activated monocytes and macrophages are the main source of TNF-α(38,41,47), and that an increase on the prostaglandin E2 observed in patients with CHF could stimulate macrophages to produce TNF-α(41,50). Other evidences indicate that in the CHF condition, this cytokine is activated regardless the inflammatory situation and the cause of the disease, suggesting that the increase on the TNF-α production is more associated to the presence of CHF-imposed limitations instead of being the causative agent of this condition(41-45).

Thus, the mechanisms that modulate the TNF-α production in this condition are not fully known and, on the other hand, it seems to play a complex role as a communication “link” between several regulatory systems(38,41,47).

Effects of the physical training on the chronic heart failure

A meta-analysis on the trial of patients after myocardial infarction demonstrated a reduction of 25% on the total number of deaths among patients submitted to aerobic physical training program(4).

The physical training performed through aerobic exercises is currently considered as the base of heart rehabilitation programs and an important non-pharmacological way of treatment and allows minimizing the risk factors that predispose individuals to cardiovascular diseases(3,3). It is generally employed as a multidimensional rehabilitation program that begins within two to six weeks after discharge from hospital, with exercise sessions such as walks, runs, swimming, among others(2,4,46).

The final objectives of these programs are to increase the physical and psychological capacities of the individual, to control the cardiorespiratory symptoms, to decrease the risk of sudden death and the relapse of infarctions in such way to reestablish a normal daily life routine, especially activities interrupted due to the disease(4). On the other hand, patients with chronic obstructive pulmonary disease, class IV functional heart failure, cachexia, complex ventricular arrhythmias and osteoarticular pathologies cannot be submitted to regular practice of physical activities, and the utilization of physical training programs is inadequate in these cases(3,4).

The potential benefits of the aerobic training performed at intensities from light to moderate (40-85% of the VO2 peak) 3 to 5 days a week during 20-60 minutes(3,4) in post-infarction patients have been extensively reported(1,3,46). The light to moderate aerobic training program contributes to the improvement on the cardiovascular system with lower heart rate and blood pressure within the same workload(3,4,46). This leads to a peripheral adaptation in the high-density and low-density cholesterol balance (HDL/LDL) and to effects on the angina threshold. Beneficial effects on the carbohydrate metabolism, blood viscosity and reduction on the total body mass have also been described(4).

Patients with cardiovascular diseases submitted to light to moderate intensity aerobic training present enhanced O2 uptake maximum capacity (VO2 max), particularly when previously sedentary. This improvement seems to be initially due to the peripheral adaptations on the active skeletal musculature in function of an increase on the O2 venous-arterial difference(39). Another important effect is the higher myocardial O2 supply due to the increase on the blood flow to the coronary arteries and the reduction both initial and recurrent on the risk of myocardial infarction(3,4).

The light to moderate intensity aerobic training may also increase the oxygen supply to the myocardium due to the increase on the blood flow through the coronary artery. These adaptations include an increase on the myocardial capillary density, enlargement of the main coronary arteries and enhance on the development of collateral vessels in the presence of a progressive or chronic occlusion of the coronary artery(3).

Beneficial effects on the carbohydrate metabolism, blood viscosity and reduction on the total body mass have also been described(4).

Besides the cardiovascular benefits induced both by adaptations in function of the heart’s pumping and by peripheral adaptations, the physical training seems to have a modular effect in pathological conditions that present an abnormal chronic inflammatory condition, especially due to the high expression of proinflammatory cytokines, soluble adhesion molecules and chemoattractive factors(40,49,52).

Batista Jr.(52) using Wistar rats with chronic myocardial infarction demonstrated a chronic increase on the chemotaxis index and on the production of TNF-α through macrophages from the peritoneal cavity of these animals, demonstrating a chronic activation of these cells. On the other hand, the moderate aerobic training in treadmill (60% of the VO2 peak) with 10-week duration 5 times a week during 1 hour a day was capable to revert this situation. Adamopoulos et al.(40) demonstrated a reduction on the plasma concentration of peripheral markers of inflammation (cellular-1 soluble adhesion molecule, vascular cell-1 soluble molecule, chemoattractive protein for macrophages 1) after 12 weeks of aerobic training in cycle ergometer (70-80% of the HR peak) 5 times a week during 1 hour a day in patients with moderate to severe heart failure (New York Heart Association, functional class II-III), suggesting a correlation between the enhanced exercise tolerance and the attenuation of the inflammatory process due to a possible reversion on the harmful effects caused by the endothelial dysfunction presented in the heart failure condition. However, a significant correlation cannot establish a cause-effect relation, and other mechanisms have been proposed in order to explain the beneficial effects obtained through physical training programs in individuals with heart failure. The reduction on the plasma TNF-α concentration, IL-6 and its respective soluble receptors has also been demonstrated in individuals with chronic heart failure submitted to an aerobic training program(48), suggesting an attenuation on the chronic inflammatory condition mediated by a regulation on the peripheral inflammatory response(40,48,52).

Similarly, the utilization of a 4-month physical training program with aerobic exercises in cycle ergometer (90% of the anaerobic thresh-
old-H) performed 3 times a week during 20 minutes along with endurance exercises (50% of the MR and 9 exercises per session) during 30 minutes presented a reduction on the sTNFR I and II concentrations in patients with CHF, suggesting possible effects of the simultaneous use of aerobic and endurance exercises on the attenuation of the inflammatory condition (49).

Alterations on the neuro-immune-endocrine axis (5,7,52) and metabolic abnormalities on the muscle-skeletal (46) have been proposed in order to explain alterations that lead to exercise intolerance as well as possible mediators of their beneficial effects. Thus, the role of several regulatory systems that result in metabolic abnormalities mediated through inflammatory and hormonal dysfunctions has been demonstrated in individuals with CHF, and currently this condition has been considered as a chronic degenerative disease as a result of a multi-systemic interaction, in other words, an interface between hemodynamic, neurohormonal and immunological variables and metabolic dysfunctions. In this condition, the scientific evidences recently observed suggest that inflammatory mediators such as proinflammatory cytokines play important role both in the pathogenesis and in the development of the CHF syndrome. Thus, moderate physical training programs lasting from 3 to 6 months with 3 to 5 weekly sessions during 1 hour, besides providing a positive effect on the cardio-circulatory variables, already well-established in literature, would act as important positive immune-modulator, reverting, even partly, the inflammatory alterations as result of the CHF condition, reinforcing its non-pharmacological intervention role.

CONCLUSION

Interestingly, the adaptations to physical training demonstrated in individuals with chronic heart failure promoted a decrease on the hemodynamic and metabolic overload both in the cardiovascular and in the muscle-skeletal systems and modified inflammatory parameters, leading to a decrease on the peripheral inflammatory markers concentration, especially on the production of cytokine, remarkably the tumoral necrosis factor. This cytokine is important during the establishment and development of the inflammatory process following the development of the chronic heart failure, vital for the recovery, even partial, of the cardiac muscle functions, but mainly, harmful, when present in high concentrations in the chronic phase of the pathology. Moreover, it becomes evident that this chronic inflammatory condition plays important role on the decrease on the capacity of performing physical exercises, an important characteristic of this syndrome. Thus, considering the modulating effect of the moderate physical exercise on the TNF-α production in patients with CHF, a larger number of researches becomes necessary in order to evaluate possible alterations on the temporal production of other proinflammatory cytokines and researches aimed at evaluating the ideal type and form of exercise to be prescribed to this specific population, thus allowing the physician to prescribe regular physical exercises as part of clinical treatment of the CHF.

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REFERENCES


