# Anti-inflammatory Effect of Physical Training in Heart Failure: Role of TNF-α and IL-10

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## Abstract

Over the past 50 years, the understanding of the deteriorative changes involved in the progression of heart failure (HF), initially described as resulting from changes in salt and fluid retention, or changes in hemodynamic parameters, have changed significantly. Recently, several studies conducted in HF patients showed altered plasma (or serum) levels of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukins 1, 6, and 18, and cardiotropin-1, among other inflammatory markers. These changes were independent of HF etiology, suggesting a common pathogenic pathway. In response to these new findings, interventions to prevent and/or reduce these inflammatory changes have been proposed.

The aerobic training-induced cardiovascular benefits of physical exercises performed at intensities ranging from mild to moderate have been previously reported. Moreover, it has been shown that moderate aerobic physical training seems to be able to modulate, in the presence of an abnormal chronic inflammatory condition, the overexpression of pro-inflammatory cytokines, soluble adhesion molecules, chemoattractant factors and oxidative stress. Altogether, these data indicate a possible anti-inflammatory effect induced by physical training.

Therefore, this review aims to assess the role of physical training as an alternative non-pharmacological adjuvant to be administered in some pathological conditions in which TNF-α chronic changes are predominant, as in HF. The "anti-inflammatory effect" induced by physical training seems to be primarily mediated by IL-10.

## Introduction

Heart failure (HF) is a clinical syndrome of complex pathophysiology, which may be due to any structural or functional disorder that affects the heart, and consequently undermines the ability of the ventricles to fill up and pump blood adequately[1,2]. Dyspnea and fatigue are cardinal manifestations of HF which may limit the ability of the patient to perform physical exercise (exercise intolerance) and can lead to processes that may result in systemic pulmonary congestion and increased peripheral vascular resistance[1,3,4]. The main cardiac causes of HF are coronary artery diseases, including hypertension, dilated cardiomyopathies and heart valve diseases[1,2].

Currently, the deteriorative changes involved in the progression of HF, which were previously interpreted as arising from changes in salt and water retention or changes in hemodynamic parameters, have been described as recurring processes that culminate in local and systemic inflammatory activation[5-9], which can be evidenced by the increase in the gene expression and the production of proinflammatory cytokines, such as tumor necrosis factor α (TNF-α); interleukins 1β (IL-1β), 6 (IL-6) and 18 (IL-18 ); cardiotropin-1; CC and CXC chemokines, among other inflammatory markers, in plasma, muscle-skeletal and heart, as well as in peripheral lymphocytes of rats and HF patients. In addition to contributing to the pathophysiology and the progression of structural and functional changes in the heart muscle, these inflammatory mediators may directly lead to peripheral manifestations of the HF syndrome, especially in those changes related to a decrease in muscle mass and functional changes[10,11], among others.

Following this line of reasoning, Coats et al[7] proposed a hypothesis called "the muscle hypothesis of HF", according to which the degenerative changes are due to a reduced perfusion in skeletal muscles caused by low cardiac output, resulting in tissue hypoxia. If maintained for a long time, this tissue hypoxia and the consequent increase in the production of free radicals are a powerful stimulus for the production of pro-inflammatory cytokines (TNF-α, IL-1 β and IL-6), mediated by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), initiating a cascade of events which comprises the expression of inducible nitric oxide synthase (iNOS), skeletal muscle apoptosis and loss of muscle mass[5,11-13].

Therefore, although in recent years most studies have focused on the HF pro-inflammatory cytokines, today the anti-inflammatory cytokines, particularly IL-10, have gained prominence and may have an important role in the pathophysiology of HF[14,15]. In patients with HF, a decrease in IL-10 plasma concentration has been reported and positively correlated with a decrease in the left ventricular ejection fraction[16]. Furthermore, in animals with myocardial infarction-induced HF, the use of the rate of production of IL-10 by TNF- α (IL-10 / TNF- α rate) has recently been demonstrated as a more accurate indicator of the degree of ventricular dysfunction in that condition[14,17].

## Key Words

Exercise; heart failure; coronary artery disease; interleukins.

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Physical training, carried out mainly through aerobic exercises, has been considered as the main basis for cardiac rehabilitation programs and an important form of non-pharmacological treatment, which can achieve the established goal of minimizing the risk factors that predispose the individual to cardiovascular diseases[18,19].

Besides the cardiovascular benefits, induced both by changes in the function of the heart as a pump and by peripheral changes, physical training seems to be able to modulate, in the presence of an abnormal chronic inflammatory condition, the expression of pro-inflammatory cytokines, soluble adhesion molecules and chemoattractant factors[8,20]. The use of aerobic training on an ergometric treadmill at 70% $VO_{2peak}$ for six months was able to diminish the increased local expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) in striated skeletal muscle in patients with HF. In the same study, it was shown that this reduction was associated with a reduction in the gene expression of iNOS and the accumulation of intracellular nitric oxide (NO), suggesting that physical training should be used not only as a form of intervention to improve physical capacity (affected or not by HF), but as a therapeutic strategy with local anti-inflammatory purposes.

In this regard, several studies have shown changes in plasma concentration of IL-10 and IL-ra (IL-1 receptor antagonist) after exercise, a condition which can contribute to the anti-inflammatory milieu, and thus be an important mediator of the anti-inflammatory effects of physical training. IL-10 can act in different cell types and induces suppression of inflammatory response in several cell types[21]. Moreover, this cytokine has been postulated as the main molecule responsible for the "orchestra" of inflammatory reactions, especially the inhibition of the changes mediated by TNF- α[21,22].

Moreover, despite increasing evidence indicating the existence of a relationship between the anti-inflammatory effect of exercise and its protective and/or inhibitor effect in various clinical pictures, possible long range effects (training) are not well characterized.

Therefore, we may conclude that only recently the possible anti-inflammatory effects of physical training on the production of pro-inflammatory (TNF-α) and anti-inflammatory (IL-10) cytokines in patients with HF have been studied. On the other hand, adaptations resulting from moderate aerobic training (55% - 65% $VO_{2peak}$) may have immunomodulatory effects, especially in the production of IL-10, a condition that could be even more evident in clinical pictures that present a chronic increase in the production of these inflammatory markers. Besides, increased physical activity is critical in the adjuvant treatment of patients with HF, depending, of course, on the intensity of this reduction in the severity of the disease.

## Role of TNF-α in the progression of HF

As described above, pro-inflammatory cytokines, especially TNF-α, and other inflammatory mediators such as chemokines, play a prominent role in several levels of HF. Initially, although their release has a restoration or repair function, if maintained over time they can have an important role in the modulation of the deteriorating changes of HF[23]. These data are corroborated by other model studies data in which high levels of inflammatory mediators, such as TNF-α and nitric oxide, were experimentally induced to mimic some characteristic clinical changes of HF, such as progressive left ventricular dysfunction, pulmonary edema and cardiomyopathies[24]. Moreover, several changes detected in plasma levels show a correlation with markers of characteristic dysfunctions of HF, which are also prognostic and severity markers of HF[25,26].

Besides the changes in plasma levels, a recent study[27] showed positive correlations between TNF-α levels in the cardiac myocyte and in the hypothalamic paraventricular nucleus in rats with HF. In addition, these changes were related to a higher neurohumoral excitation in the brain cardiovascular region[28] and greater activation of the renin-angiotensin system[29], suggesting a possible interaction between these systems (renin-angiotensin system and immune system) which may modulate changes such as sodium and water retention and the cardiac remodeling process in rats with HF.

TNF-α was described in 1975 and it was initially named cachectin due to its potent cytotoxic effect against tumor cells[23,25]. It is a trimeric polypeptide (17 kDa), produced mainly by activated monocytes and macrophages, and other cells, such as lymphocytes, fibroblasts, neutrophils, smooth muscle cells and mastocytes[23,30]. This cytokine can act in almost all types of nucleated cells by two types of membrane receptors, type I (TNFR-I, p55) and type II (TNFR-II, p75), or as a soluble molecule, both biologically active[8,23].

Previous studies demonstrated the presence of both types of receptors, in the skeletal muscle[31] and in the heart muscle[8]. After translation, similarly to TNF-α, both receptors are inserted into the cell membrane. In the proteolytic cleavage, mediated by a TNF-α converting metalloproteinase (TACE), TNFRs and TNF-α are released in their soluble form. Thus, fragments of extracellular domains of both TNF-α receptors (type I and II), which can be released from the cell membrane and quantified in their soluble form (TNFR I and TNFR II) in urine and plasma, they have been described as biological activity regulators of this cytokine[32].

In physiological concentrations, TNFRs can act as a reservoir for slow release, thus increasing the half life of this cytokine[23,33]. When present in high concentrations, as in patients with severe HF (class III and IV, NYHA), TNFRs can inhibit the pathological increase of TNF- α activity, thus acting as a anti-TNF-α[8].

In 1990, Lavine et al[34] observed that HF patients had increased levels of this cytokine (115 ± 25 X 9 ± 3 U/mL) when compared to individuals without the disease. They also showed that the greater the increase, the greater the tendency of these patients to develop cardiac cachexia. Recent studies have shown high concentrations of TNF-α in individuals with cardiac cachexia and this cytokine is also an important predictor of weight loss[35].

TNF-α may be the main cause of a number of metabolic disorders in patients with HF, such as high metabolic rate[25]; decrease in blood flow to peripheral tissues and endothelial dysfunction[7,36]; activation of iNOS[11,37]; and changes in the metabolism of proteins and lipids[38]. In addition to their known thermogenic effect, high concentrations of these cytokines may be related to increased plasma concentrations of insulin, abnormalities in the metabolism of steroid hormones and

growing hormone[39], left ventricle dysfunction[5] and exercise intolerance[3,7,40].

However, little is known regarding the mechanisms responsible for inducing the increase in the production of TNF-α, and thus, some hypotheses have been proposed (Figure 1). It is known that activated monocytes and macrophages are the main source of TNF-α[23], and that an increase in the production of prostaglandin E2, observed in patients with HF, could stimulate macrophages to produce TNF-α[38]. Previous[41] studies demonstrated that macrophages from the peritoneal cavity of rats with MI-induced HF increased the production of TNF-α, and other pro-inflammatory cytokines (IL-1β and IL-6), when stimulated with lipopolysaccharide (LPS).

On the other hand, recent evidence suggested that in HF, TNF-α changes are present regardless of the inflammatory condition and the cause of the disease, suggesting that the increase in this cytokine is associated with the presence of constraints imposed by the HF, rather than HF being the cause of this condition[6,42]. Thus, in HF, the mechanisms that modulate the production of TNF-α are poorly understood, on the other hand, this cytokine seems to have a complex role, and it seems to be a between several regulatory systems[5,38].

## Role of IL-10 in the progression of HF

Due to the large number of studies that associated the role of pro-inflammatory cytokines to the pathogenesis and progression of HF, the possibility of using interventions that handle anti-inflammatory cytokines as an adjuvant therapy in patients with HF has been theorized. On the other hand, despite this therapeutic potential, only recently the role of IL-10 in HF has been the focus in studies[14,43].

Interleukin 10 (IL-10) is a homodimeric polypeptide of 17 kDa, which was initially described as a factor produced by T helper lymphocytes (type 2) with inhibitory properties in clones of T helper lymphocytes (type 1), especially in the proliferative response and the production of cytokines[21]. This cytokine is produced by a number of different cell types, especially inflammatory cells such as macrophages and T lymphocytes, in which it is the main inhibitor of cytokine synthesis and macrophage functional activity. It also inhibits the production both of the pro-inflammatory cytokines and the extracellular matrix metalloproteinases[8,21].

Its biological activity is mediated by its membrane receptor (IL-10R), which belongs to a subgroup of receptors that are similar to interferon (INF), from the Class II cytokine receptor family[21,22]. Thus, IL-10 can inhibit the production of several cytokines such as TNF-α, IL-1β and IL-6, in various cell types, and it is also self-modulated[15,21]. It also inhibits the generation of reactive oxygen species (intermediate) and increases the release of TNFR receptors, which may antagonize the effects of TNF-α[44]. Furthermore, studies have shown that IL-10 production increased in inflammatory processes, such as anemia and rheumatoid arthritis, and also in HF, exerting a predominantly immunomodulatory role in such conditions[15].

Bolger et al[45] demonstrated that IL-10 inhibits the secretion of TNF-α in isolated peripheral blood mononuclear cells (ex vivo) of HF patients (functional class III, NYHA). In another chronic inflammatory condition such as atherosclerosis in mice (C57BL/6J, IL-10 knockout mice), IL-10 has also been described by its protective (anti-inflammatory) properties in delaying the progression of the disease, since high levels

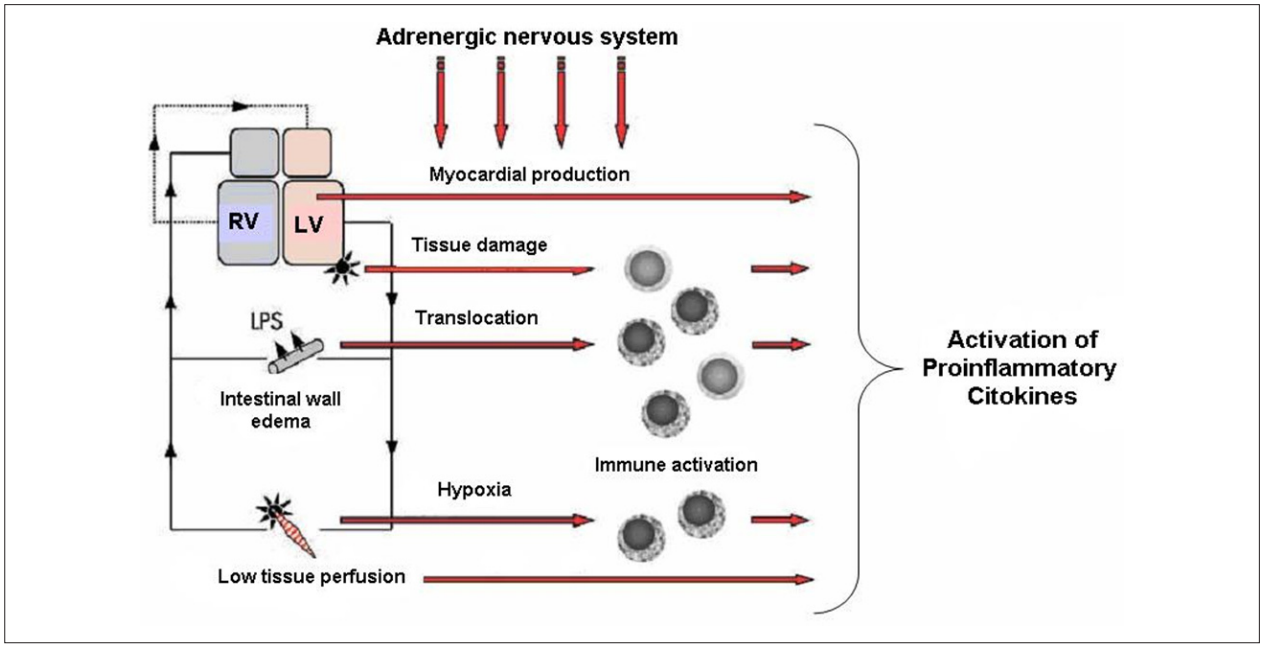


*Figure 1 - Hypotheses about the origin of pro-inflammatory cytokines and the activation of the immune system in HF. These can be mutually complementary. The myocardium itself is capable of secreting pro-inflammatory cytokines which can be stimulated by adrenergic activation. The same can occur with the skeletal muscle. Myocardial tissue injury (for example), myocardial infarction, translocation of bacteria and peripheral tissue hypoxia, may all lead to the activation of peripheral leukocytes, which may eventually lead to the activation of pro-inflammatory cytokines. LPS: lipopolysaccharide; LV: left ventricle, RV: right ventricle. Adapted from[9].*

of IL-10 were associated with a reduction in apoptosis and the expression of iNOS-1 mRNA in the endothelial cells, macrophages and T lymphocytes of these animals[46].

As explained above, the IL-10 acts in a predominantly anti-inflammatory and modulatory manner in the inflammatory response, a condition that seems to be even more evident in chronic inflammatory diseases, especially in those in which TNF-α seems to act in a significant manner (ex.: rheumatoid arthritis, multiple sclerosis, inflammatory disease of the digestive tract, HF, among others)[45,47,48]. Accordingly, the study of Gullestad et al[43] demonstrated that the intravenous infusion of immunoglobulin, a therapy used in immune system-mediated diseases, such as Kawasaki syndrome, dermatomyositis and multiple sclerosisincreased IL-10 levels in patients with HF (dilated cardiomyopathy and ischemic myocardial disease). Moreover, this increase showed a positive correlation with the improvement in the ejection fraction of the left ventricle in patients with HF, as well as in animals with MI-induced HF. The production of IL-10 by TNF-α (IL-10/TNF-α rate) in the left ventricle proved to be a more accurate indicator of the degree of ventricular dysfunction in this condition[48].

Recently, the study of Yu et al[49] showed that peripheral manifestations of MI-induced HF in rats can be alleviated by reducing the intensity of the inflammatory/immune response in the brain. In these animals, the change in balance of pro and anti-inflammatory cytokines induced by the administration of an adenoviral vector encoding the gene for human IL-10, produced "beneficial" effects in the severity of HF, such as an improvement in left ventricular function and a decrease in plasma norepinephrine levels, and less prominence in the remodeling of the right ventricle and pulmonary vascular congestion. Another study, which administered rhIL-10 in vivo showed the same effect[45]. In addition, Yamaoka et al[15] demonstrated that mononuclear leukocytes collected from patients with HF (functional class II-IV, NYHA) had a greater number of IL-10 receptors in their cell membranes.

Altogether, these studies suggest an important role of IL-10 in the pathophysiology of HF, mainly due to its modulating effect in the synthesis and secretion of TNF-α. Thus, this cytokine is gaining a prominent role as a therapeutic option. Moreover, the IL-10/TNF-α rate may have a cumulative role in the evaluation of the deterioration and progression of the HF. On the other hand, more studies are needed for the understanding of the molecular mechanisms that modulate the events above described.

### Effect of aerobic training on pro-inflammatory cytokines in HF

It is now well established that physical training is directly related to the functional improvement of quantitative physical capacity, such as in $VO_{2peak}$, in endothelial function and consequently in the quality of life of patients with HF[11,50-52]. Other variables associated with a worse prognosis, such as an improvement in sympathetic and neuro-hormonal activity and peripheral hypoxia, have also been reported as being positively modulated by physical training[53]. Another aspect to highlight is its direct effect on the reduction in submaximal heart rate (during exercise) and at rest[50]. Consequently, physical training has been recommended by medical guidelines[1,18] as a component in therapeutic rehabilitation programs for patients with controlled HF.

Besides the benefits already mentioned, recently Adamapoulus et al[54] showed a reduction in plasma concentration of peripheral inflammatory markers (soluble cell adhesion molecule-1, soluble vascular cell molecule-1 and macrophage chemoattractant protein-1) after 12 weeks of aerobic training on a cycle ergometer (70-80% $HR_{max}$), five times a week for one hour per day in patients with moderate to severe HF (NYHA, functional class II - III). Thus, it suggests a correlation between improvement in exercise tolerance and the attenuation of the inflammatory process due to a possible reversal of the deleterious effects caused by the endothelial dysfunction that is present in HF. Accordingly, Batista et al[20] demonstrated the reversal of some inflammatory parameters in peritoneal macrophages and mesenteric lymph nodes in rats with MI-induced HF a program of moderate aerobic training (running on a treadmill) with duration of 10 weeks, reaching values close to those found in control groups. However, the evidence of a significant correlation cannot establish a cause and effect relationship, and other mechanisms have been proposed to explain the "beneficial" effects mediated by physical training in individuals with HF.

A reduction in plasma concentration of TNF-α, IL-6 and their receptors in soluble form have also been demonstrated in individuals with HF undergoing an aerobic training program[55], suggesting a reduction in the chronic inflammatory condition, mediated by a regulation in peripheral inflammatory response[56,57]. However, despite the marked restorative and/or anti-inflammatory effect of exercise in these conditions, little is known about the possible mechanisms by which aerobic training can modulate this process[57].

Following this line of reasoning, Gielen et al[58] published the first study that showed an increase in the local expression of pro-inflammatory cytokines in biopsy samples from skeletal muscle in subjects with HF. Moreover, this increase was not shown when the parameter measured was the plasma concentration of these cytokines, and thus it has been speculated that the local inflammation preceded the detected plasma changes. In the same study, the aerobic training in an ergometric treadmill at 70% $VO_{2peak}$, for six months, reduced this increased local expression because it showed that this reduction was associated with a reduction in the expression of the iNOS gene and the intracellular accumulation of NO, therefore suggesting that physical training should be used not only as a form of intervention aiming at improving physical capacity (affected or not by HF), but also as a therapeutic strategy with local anti-inflammatory purposes.

More recently, the same group of authors showed that the anti-inflammatory effect induced by aerobic training in the expression and production of cytokines (TNF-α, IL-1β, IL-6) and iONS, which were associated with an improvement in the maximum activity of cytochrome c oxidase enzyme (COX) and in $VO_{2peak}$, suggests that the improvement in the inflammatory parameters was based on an improvement in skeletal muscle oxidative metabolism in patients with HF[11].

A reduction in plasma concentration of TNF-α, IL-6 and their receptors in soluble form have also been demonstrated in

individuals with HF undergoing an aerobic training program[55], suggesting a reduction in chronic inflammation, mediated by a regulation in the peripheral inflammatory response[54,55]. Similarly, a program of four months of physical training with aerobic exercises on a cycle ergometer (90% of anaerobic threshold-I), three times a week for 20 minutes, along with resistance exercises (50% of repetition maximum and nine exercises per session) for 30 minutes, showed a reduction in the concentration of TNFRs I and II in patients with HF, that suggests possible effects of the simultaneous use of aerobic exercises and resistance exercises on the attenuation of inflammation[56].

Therefore, recently accumulated scientific evidence suggests that inflammatory mediators such as pro-inflammatory cytokines, play an important role both in the pathogenesis and the development of the HF syndrome. Thus, besides exerting a positive effect on cardiocirculatory variables, which is well established in the literature, moderate physical training programs lasting from three to six months, with three to five one-hour sessions per week, act as an important positive immunomodulator, thus, albeit partially, reverting the inflammatory changes that arise from HF and reinforcing their role as a non-pharmacological intervention.

## Role of physical training as an anti-inflammatory strategy

In recent years, several studies have suggested that an acute session of physical exercise has anti-inflammatory effects, especially immediately after the exercise; the main cytokine involved in this modulation is IL-6[59,60]. This anti-inflammatory effect is characterized by a subsequent increase in plasma levels of the cytokines IL-10, ILra and the soluble TNF receptors I and II, induced by the IL-6 after a session of physical exercise[60]. Moreover, this effect is more evident in some clinical pictures, such as atherosclerosis, type II diabetes, obesity and HF, especially those characterized by chronic low grade inflammation, a condition that is characterized by two or three-fold systemic increase in the levels of pro-inflammatory cytokines and C-reactive protein[61] (Figure 2).

Furthermore, the profile of cytokine production that occurs during and immediately after exercise is dependent on many factors such as population (sedentary, presence or absence of disease, etc.); intensity or duration of exercise; availability of glucose; and time of sample collection[62].

Therefore, the proposed hypothesis is that the regular practice of physical exercise, organized as a training program, has an anti-inflammatory effect induced by acute multiple sessions, which leads to protection against chronic inflammatory conditions, especially by reducing the levels of pro-inflammatory cytokines and C-reactive protein[60,63]. Despite the obvious correlation, little information has been produced until now regarding the possible mechanisms that explain the cause-effect relationship between physical training and the reduction in these markers levels[59]. Also, the origin of this systemic change is not well characterized. However, it has been proposed that white adipose tissue[60] and peripheral blood mononuclear cells (especially lymphocytes) may be the main source of cytokines[59,63].

To evaluate this possible anti-inflammatory effect, Starkie et al[64] showed a reduction in the levels of TNF-α induced by the experimental model in a low grade systemic inflammation experimental model, which was induced by the intravenous administration of endotoxin (Escherichia coli) to healthy subjects, three hours after a session of aerobic exercise on a cycle ergometer (75% $VO_{2peak}$)α. The same suppressive effect induced by physical exercise was also demonstrated in knockout mice for TNF-α receptor type I and II, in restoring the increased levels of TNF-α[65]. However, the possible mechanisms that modulate this "beneficial" effect have not been established.

## Possible mechanisms involved in the anti-inflammatory response after exercise

Although the importance of pro-inflammatory mediators in the pathogenesis of HF was confirmed in the last few years, only recently it was noted that this was not accompanied by a corresponding increase in anti-inflammatory cytokines such as IL-10 and in transforming growth factor (TGF), resulting in an imbalance in the levels of cytokines (pro vs. anti-inflammatory).

The pharmacological treatment that is conventionally used in HF with an impact on mortality (e.g. β-blockers, angiotensin-converting enzyme inhibitors, and spironolactone) has shown slight effects in the reduction of inflammatory markers in these patients, and thus, an immunomodulatory therapy has been proposed and tested in combination with the conventional treatment as an adjuvant option[66]. The adjuvant therapy (eg, pentoxifylline, intravenous immunoglobulin, thalidomine, infliximab and statins) has shown promising results in small studies, but only in relation to outcomes of minor clinical relevance, such as an improvement in the biochemical profile[66]. Traditionally, patients with HF are excluded from studies in which the effects of statins are tested in clinical events. However, a recent study[67] evaluated the effect of statin (rosuvastatin) in patients over 60 years of age with moderate to severe systolic heart failure. In the study, the use of 10mg/day of rosuvastatin had a statistically significant effect in reducing the levels of LDL-cholesterol and inflammatory markers such as C-reactive protein.

In this aspect, as described above, the use of physical training as an adjuvant therapy, besides restoring cardiovascular function changes that occurred because of the HF (which does not seem to occur in the therapeutic adjuvants mentioned above), proved to be an important immunomodulatory agent. On the other hand, despite increasing evidence that demonstrates the importance of IL-10, mainly due to its anti-inflammatory action, few studies have evaluated the possible effects of physical training in modulating the local production of IL-10, which has an important role in the pro/anti-inflammatory balance, especially in conditions in which there is an imbalance in this relationship.

Therefore, the proposed hypothesis is that the regular practice of physical exercise, organized as a training program, has an anti-inflammatory effect induced by acute multiple sessions, which leads to protection against chronic inflammatory conditions, especially by reducing the levels of pro-inflammatory cytokines and C-reactive protein[60,63]. However, the possible mechanisms modulating this "beneficial" effect are not established and could be related

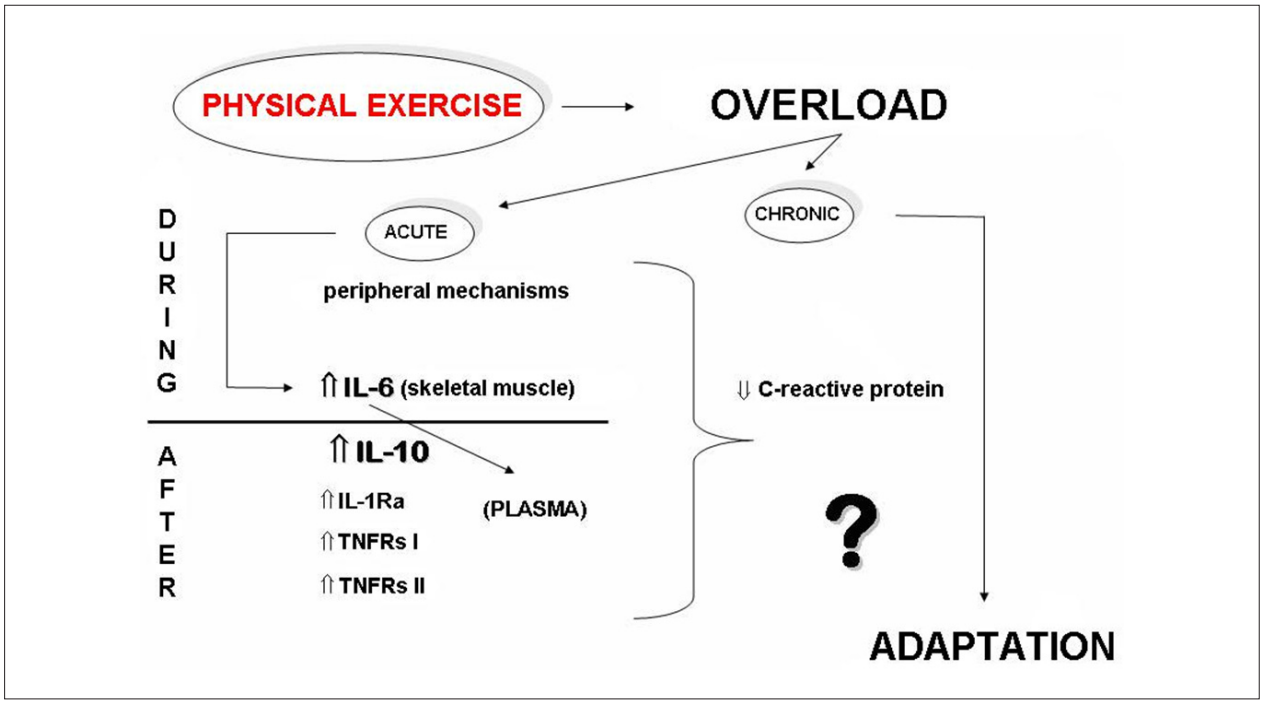


*Figure 2 - Acute and chronic effect of exercise (training) on plasma levels of anti-inflammatory cytokines, mediated by interleukin 6 (IL-6), secreted by skeletal muscle (acutely). Physical training leads to a reduction in the levels of C-reactive protein (CRP), a condition most evident in clinical pictures that show high levels of this acute phase protein (chronically). Moreover, it is assumed that the sum of the acute effects leads to a prevalence of anti-inflammatory cytokines, particularly interleukin 10 (IL-10). IL-1ra: IL-1 antagonist receptor; TNFRs-I: TNF-α receptors type I; TNFRs-II: TNF-α receptors type II.*

both to an improvement in conditional physical capacity and a direct anti-inflammatory effect.

As already described, IL-10 modulates inflammatory processes by eliminating the production of pro-inflammatory cytokines, especially TNF-α, which is transcriptionally modulated by NF-κB. Furthermore, a recent study showed that in rats, the aerobic training on an ergometric treadmill increases the activation of this system, notably by reducing the levels of IκBα (NF-κB system inhibitory protein) and increasing the phosphorylation of IKK (an enzyme that degrades the IκB protein complex)[68]. It is also noteworthy that, despite evidence showing that IL-10 inhibits a number of changes mediated by TNF-α, especially those involving the activation of NF-κB, and that aerobic training increases the activation of this system, none of these studies evaluated the effect of training on a condition in which NF-κB is activated, such as HF. Moreover, in patients with diabetes type II, a program of aerobic training on an ergometric bicycle (70% $VO_{2peak}$, four times a week for eight weeks) showed an increase in protein levels of IκBα and β in both groups (diabetic and control of the same age) which was followed by a reduction in protein levels of TNF-α[69]. Therefore, the possible mechanisms concerning the effect of physical training in HF, which modulates the production of TNF-α by increasing IL-10, is shown in Figure 3.

## Final considerations

Given the above, data from the literature support the anti-inflammatory hypothesis. Notably, IL-10 protein appears to be affected by physical training (mainly aerobic) and may act as an important "trigger" in the reduction and/or modulation of the inflammatory response in HF. Also, in addition to an increase in the local production of IL-10, induced by physical training, this effect could have a systemic impact, reducing or even preventing the increase in plasma levels of pro-inflammatory cytokines, a condition that is related to increased severity of the disease, in HF. Studies that evaluate the effect of controlled physical training in relevant clinical outcomes, such as mortality in HF patients, are needed to incorporate this treatment modality into clinical practice.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

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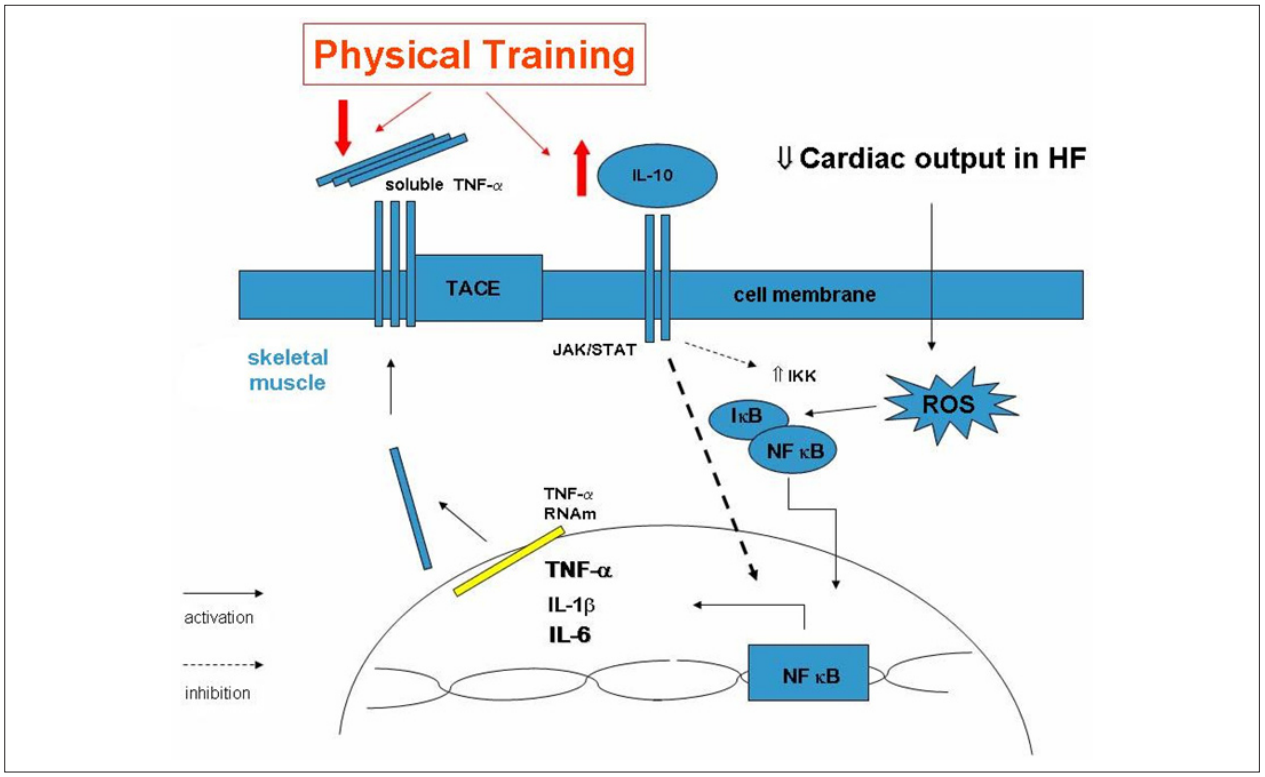


*Figure 3 - Hypothetical effect of physical training, by an increase in IL-10, on modulating the inflammatory processes by eliminating the production of pro-inflammatory cytokines, especially TNF-α, which is transcriptionally modulated by the nuclear transcription factor kappa (κ) B system NF-κB; IκBα: NF-αB system inhibitory protein; IKK: enzyme that degrades the protein complex IκB; TACE: TNF-α converting metalloproteinase; ROS: reactive oxygen species.*

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