Immunomodulatory Effects of Physical Training in Chronic Heart Failure

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Chronic heart failure (CHF) is a complex syndrome caused by cardiac muscle dysfunction secondary to myocardial injury or mechanical overloading, and characterized by signs and symptoms related to inadequate tissue perfusion, fluid retention and neurohormonal reactions[1]. There is strong evidence that, although cardiac dysfunction plays a pivotal role in the development of CHF, multiple abnormalities also occur in peripheral tissues. Crucially, heart failure involves neuroendocrine dysfunction, with the activation of opposing vasoconstrictor and vasodilator hormone systems[2]. It is also associated with generalized disturbances of metabolic and cellular function, and ultimately with cachexia[1,2]. The structure and function of many different organs may be affected. Not only is there cardiac remodeling and fibrosis, but changes also occur in the lung, kidney, skeletal muscle and vascular wall, even in the early stages of CHF[2].

The overactivation of several neurohormonal systems and overproduction of biologically active molecules such as norepinephrine, angiotensin II, aldosterone, endothelin-1 and proinflammatory cytokines are important pathophysiological parameters that contribute to disease progression in the failing heart[1,2]. Especially, the existence of an abnormal inflammatory response, mediated mainly by proinflammatory cytokines and other cytokine-related factors, contributes to some aspects of the syndrome phenotype, such as the adverse left ventricular remodeling, endothelial dysfunction and peripheral myopathy[3-5]. Deleterious effects of inflammatory cytokine cascade on cardiovascular system of patients with CHF are summarized in table 1.

Proinflammatory cytokines (i.e. TNF-α, IL-1 and IL-6) which are elevated into circulation of CHF patients, cause myocardial and endothelial dysfunction in CHF, either by increasing the production of oxygen free radicals and expression of inducible nitric oxide synthase (iNOS) or by triggering apoptosis in myocardial and endothelial cells through oxidative stress[4-6].

IL-6 and related cytokines have also been implicated in the development of cardiac hypertrophy, through stimulation of their common receptor gp130 expressed in cardiac myocytes[7]. Proinflammatory cytokine hyperactivation is also associated with increased gene expression of iNOS and decreased gene expression of anabolic peptide insulin-like growth factor-1 (IGF-1) in the skeletal muscle of patients with CHF, leading to attenuation of mitochondrial energy transfer (and, thus, attenuation of skeletal muscle contractile performance) and/or skeletal myocyte apoptosis[8-10]. These deleterious, central and peripheral effects may be important pathophysiologic events associated with the impaired exercise capacity of patients with heart failure[1,4,5,8-10].

Furthermore, increased circulating levels of chemotactic cytokines (C-C chemokines), such as MCP-1 and MIP-1α, have been recently found in CHF[11]. These

Table 1. Adverse biological effects of inflammatory cytokine cascade in chronic heart failure.

I. HEART
   – Promotion of left ventricular remodeling
   – Depression of cardiac contractility
   – Abnormalities of intracellular calcium handling
   – Cardiomyocyte hypertrophy
   – Cardiomyocyte apoptosis
   – Cardiac fibrosis

II. VASCULATURE
   – Progression of atherosclerosis
   – Oxidative stress
   – NO impairment
   – Vasoconstriction
   – Endothelial cell apoptosis
   – Advese vascular remodeling

III. SKELETAL MUSCLE
   – Decreased skeletal muscle blood flow
   – Anabolic/catabolic imbalance
   – Inhibition of proteinosynthesis
   – Skeletal muscle cell apoptosis
   – Cachexia

molecules are potent chemoattractants of mono-cytes and lymphocytes, with particularly high concentrations in those with the most severe heart failure[11,12]. Chemotactic cytokines may represent not only a "new" parameter of enhanced immune activation in CHF but may also reflect an important pathogenic mechanism in the development of this syndrome. Increased MCP-1 secretion from endothelial and smooth muscle cells may lead to infiltration of monocytes into the arterial wall and generation of reactive oxygen species in monocytes, which may be involved in the pathogenesis of atherosclerosis and increased apoptosis of cardiomyocytes and endothelial cells observed in patients with CHF[11-13]. On the other hand, human monocyte-endothelial cell interaction induces synthesis of inflammatory cell colony - stimulating factors, such as M-CSF and GM-CSF, which play an important role in the pathogenesis of atherosclerosis and inflammation by stimulating a range of functional activities of mature neurotrophils, monocytes and eosinophils including regulation of leukocyte adhesion, augmentation of surface antigen expression, superoxide anion generation and enhancement of cytokine production[14]. In the case of GM-CSF, we have also demonstrated elevated levels of this inflammatory factor in CHF, which are associated with the hemodynamic deterioration and neurohormonal activation characterizing this syndrome[15]. Finally, cytokines and oxygen free radicals induce the expression of endothelial adhesion molecules such as ICAM-1 and VCAM-1. These adhesion molecules are cleaved into the circulation by activated endothelial cells and can be measured as "soluble adhesion molecules" (sICAM-1 and sVCAM-1). There is growing evidence that CHF is associated with elevated soluble adhesion molecules which may represent a marker of endothelial activation or damage[16,17].

On the other hand, experimental and clinical data suggest that physical training is an important therapeutic approach in the management of patients with moderate to severe CHF. Recent studies have focused on the effects of training programs on skeletal muscle oxidative capacity in patients with moderate to severe CHF and found significant increases in the total volume density of mitochondria and volume density of cytochrome *c* oxidase-positive mitochondria independently from muscle mass or peripheral blood flow[18]. Even more recently, evidence is provided that regular physical exercise improves both basal endothelial NO formation and agonist-mediated endothelium-dependent vasodilation of the skeletal muscle microvasculature in patients with CHF by increasing expression of endothelial NO synthase and preventing the production of vasoconstrictor prostanoids and free radicals[19]. Training-induced improvement in endothelium dysfunction is associated with a significant increase in exercise performance and a notable improvement of left ventricular diastolic function[18,20]. Restoration, at least partially, of endothelial function with physical training may contribute to the redistribution of skeletal muscle blood flow with a preferential supply to oxidative muscles during submaximal exercise, thus explaining the increase in oxidative enzyme capacity of the working skeletal muscle observed in patients with CHF, which is closely related to the improved exercise tolerance after physical training[21,22].

Whatever the potential mediator of the positive effects of exercise training on the exercising muscle, the resolution of skeletal muscle abnormalities may be responsible for the reduced activity of the exaggerated muscle ergoreflex, thereby improving the abnormal responses to exercise (heightened sympathetic, vasoconstrictor and ventilatory drives) characteristic of CHF[23].

Additionally, reversal of autonomic derangements, by increasing the parasympathetically mediated component of heart rate variability, has been shown with physical training in patients with CHF[24].

The European Heart Failure Training Group[25] have reviewed the progress of 134 stable CHF patients, studied in randomized controlled trials of physical training, and have reported a good correlation between training-induced beneficial changes in autonomic parameters (chronotropic responsiveness, norepinephrine at peak exercise and standard deviation of heart rate variability) and improvement in exercise performance. These correlations might be reflecting the close relationship of increased fitness to reduced heart rate and norepinephrine spillover and increased heart rate variability. Thus, there may be a beneficial feedback between improvement in cardiovascular function and shifts in autonomic balance from sympathetic to vagal predominance.

Physical training may improve not only physical fitness but also prognosis, as has been suggested in patients with ischaemic heart disease without heart failure, perhaps by partially correcting abnormalities associated with increased mortality[26-28], such as reducing norepinephrine spillover and improving exercise tolerance and heart rate variability measures in the time and frequency domain. Reduction in the adrenergic and increase in the vagal tone have been recently proposed as the main mechanism underlying the favourable outcome in the only, so far, study translating a sustained improvement in functional capacity and quality of life into a better clinical outcome after long-term moderate exercise training[29].

On the other hand, it is known that an intense physical exercise induces an inflammatory reaction as demonstrated by the delayed increase in blood of acute phase proteins and among them of C-reactive protein[30]. There is also evidence for a diminished acute phase reaction due to regular exercise suggesting a suppression of this inflammatory response through exercise training[30]. Larsen et al. have also reported that there is a modest negative correlation between IL-6 plasma levels and skeletal muscle fiber thickness at baseline, suggesting that proinflammatory cytokines may be involved in the pathogenesis of the CHF related skeletal myopathy[31]. The same group showed that 12-week aerobic exercise training causes a significant reduction of TNF-α plasma levels and a notable increase of skeletal muscle capillary density, permitting better flow reserve of exercising muscles in patients with moderate CHF[32]. These training-induced beneficial changes were associated with the increase in the 6-min walk test (as a marker of exercise capacity) and the improvement of functional status of CHF patients. Further-
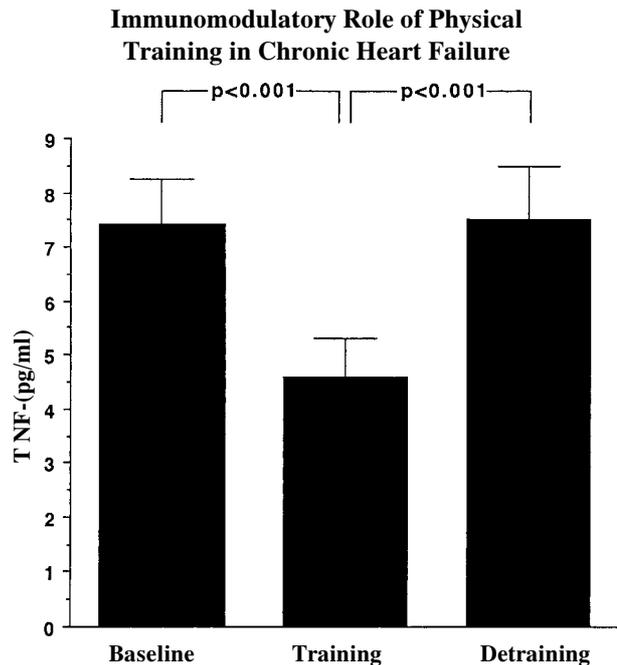

Immunomodulatory Role of Physical Training in Chronic Heart Failure

Figure 1. Effects of physical training on circulating proinflammatory cytokine tumor necrosis factor (TNF)-alpha. Note the decrease in this cytokine with training in patients with chronic heart failure (modified from Adamopoulos et al., J Am Coll Cardiol 2002).

more, programs of physical training by causing sustained, pulsatile increases in peripheral blood flow, affect the release of pronstaglandins in the skeletal muscle microvasculature[33], induce the expression of constitutive NOS (cNOS) and cytosolic superoxide dismutase[34], a free radical scavenger, and enhance Ca^{++} influx in endothelial cells, which is necessary for both NO and prostaglandin synthesis[35,36]. Additionally, our group's studies[37,38] have shown that an exercise training program intervenes in the various stages of inflammatory and apoptotic processes in patients with CHF, by reducing not only the major proinflammatory cytokines TNF-α (Figure 1) and IL-6, which enhance the cytokine cascade and are potent inducers of apoptosis, but also the soluble receptors of TNF-α and IL-6, which are products of a monocyte-myocyte/endothelial cell interaction and biological modulators of circulating cytokine actions, and finally, soluble apoptosis signaling molecules sFas Ligand (sFasL) (a newly discovered potent cytokine that is homologus to TNF-α and induces apoptotic cell death by binding to its transmembrane receptor Fas through the activation of caspases) and sFas (a soluble cellular receptor which represents an important signal for the initiation of the apoptotic process into cardiovascular system and
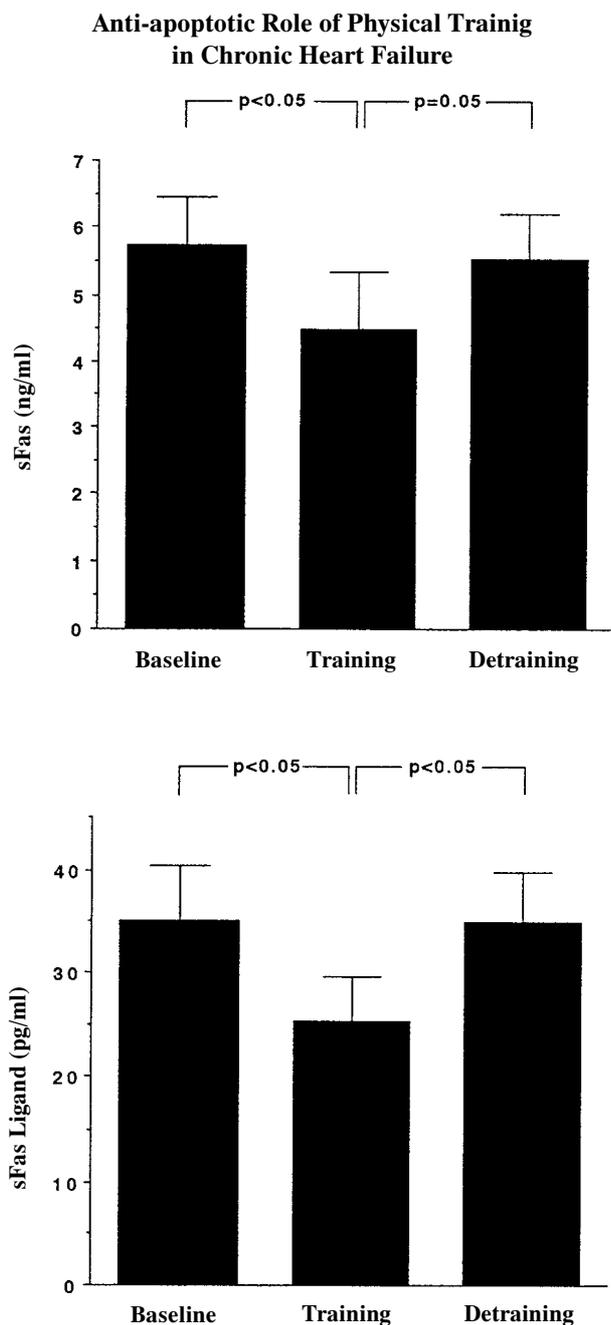
Anti-apoptotic Role of Physical Trainig in Chronic Heart Failure

Relation Between Increment in Exercise Tolerance Against Reduction in Cytokine-Apoptosis Activity
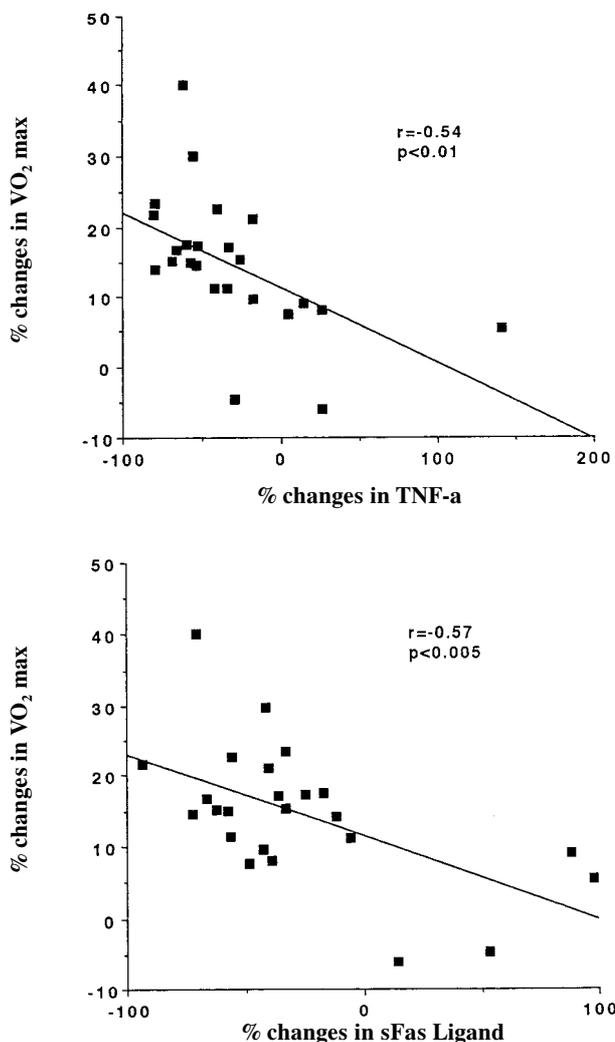

Figure 3. Correlations between training-induced changes in peak oxygen consumption (VO_2 max) and reductions in tumor necrosis factor (TNF)-alpha (top) and sFas Ligand (bottom) levels in patients with chronic heart failure (modified from Adamopoulos et al., J Am Coll Cardiol 2002).

Figure 2. Effects of physical training on soluble apoptosis mediators soluble Fas (sFas) (top) and sFas Ligand (bottom). Note the decrease in these soluble apoptosis variables with training in patients with chronic heart failure (modified from Adamopoulos et al., J Am Coll Cardiol 2002).

may have prognostic value in the syndrome of CHF) (Figure 2). In the same patient population, significant correlation was found between physical training program-induced improvement in patient exercise capacity and the respective reduction in TNF-α and sFasL plasma levels[37,38] (Figure 3). These ob-

servations suggest that exercise training may exert its beneficial effects on functional status of CHF patients at least partially, by suppressing the proinflammatory cytokine activation characterizing the progress and clinical deterioration of CHF.

Furthermore, we have recently reported[39,40] that exercise training programs reduce peripheral inflammatory factors (i.e. inflammatory cell growth factor GM-CSF; chemotactic cytokine MCP-1; soluble cellular adhesion molecules sICAM-1 and sVCAM-1), which are representative markers of macrophage-endothelial cell adhesive interaction and basal parts of complex inflammatory cytokine network in
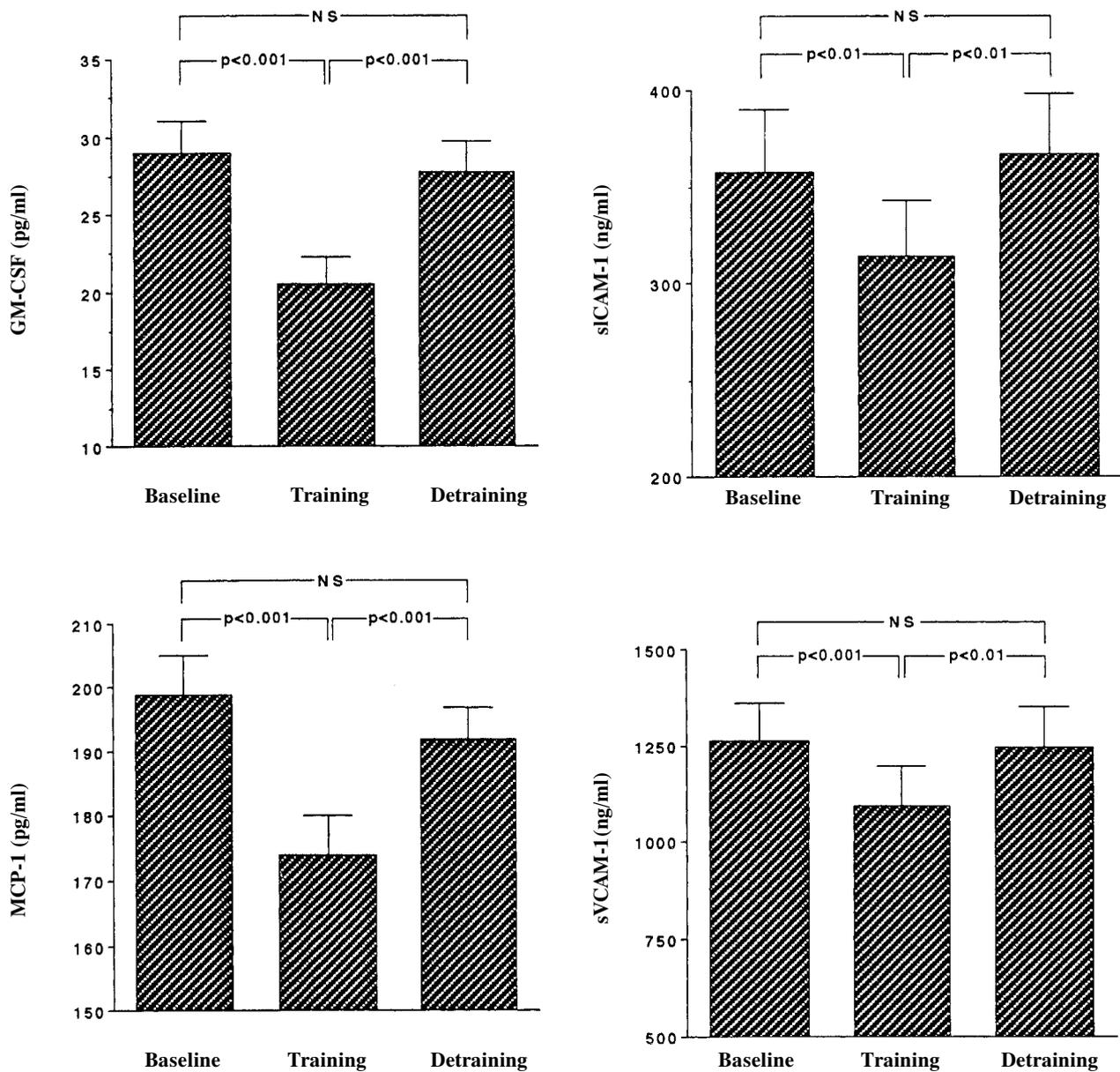
Figure 4. Effects of physical training on inflammatory markers granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage chemoattractant protein-1 (MCP-1) as well as on soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1). Note the significant reduction of GM-CSF (a, upper left panel), MCP-1 (b, lower left panel), sICAM-1 (a, upper right panel) and sVCAM-1 (b, lower right panel) (modified from Adamopoulos et al., Eur Heart J 2001).

CHF (Figure 4). Training–induced changes in soluble cellular adhesion molecules were also significantly correlated with the respective improvement in endothelial function and clinical performance of CHF patients[40] (Figure 5). This indicates that peripheral inflammation may underlie the impaired exercise capacity seen in CHF and that training-induced improvement in exercise tolerance may be attributed to the attenuation of the peripheral inflammatory process, possibly via reversing the deleterious effects of endothelial dysfunction. Although persistent cytokine activation may be a secondary event following the neurohormonal and hemodynamic abnormalities of CHF, and large clinical trials (RENAISSANCE, RECOVER) have failed to shown beneficial effects of anti-cytokine
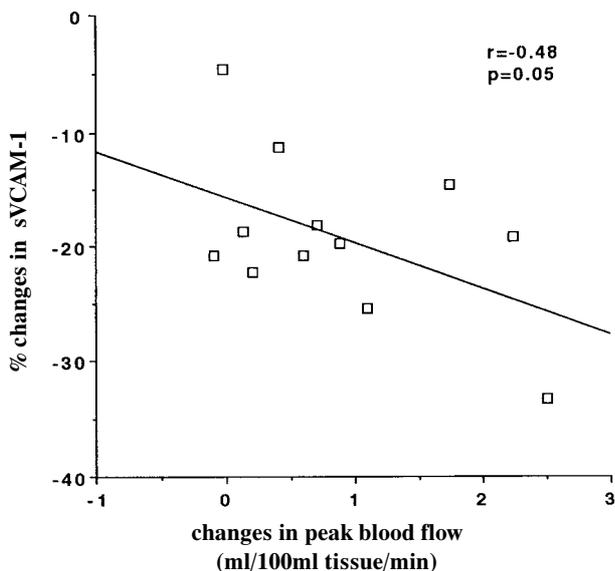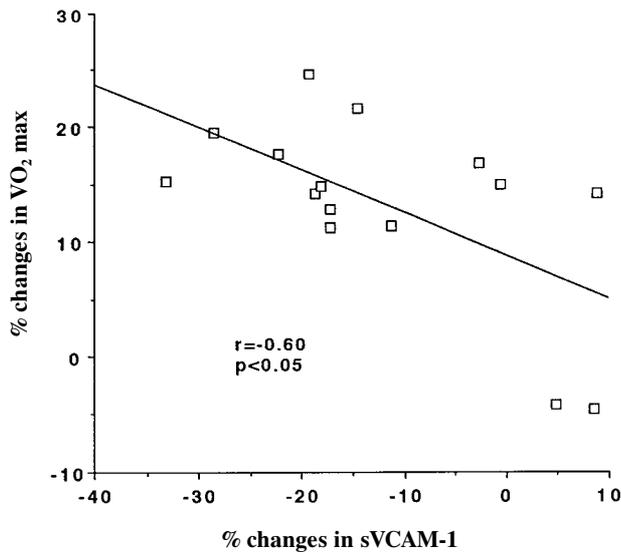
Figure 5. Correlations between training-induced changes in VO_2 max and reduction in sVCAM-1 (top) levels, as well as between training-induced increase in peripheral blood flow (improvement of endothelial function) and the respective reduction of sVCAM-1 (bottom) levels in patients with chronic heart failure (Adamopoulos et al., AHA Scientific Sessions 2001).

agents on the clinical status and prognosis of CHF patients, however immunomodulatory strategies in addition to optimal cardiovascular treatment regimens, may be promising therapeutic modalities in the management of the syndrome[41,42,43]. Physical training therefore, by virtue of its anti-inflammatory and anti-apoptotic effects, seems to beneficially

Table 2. Immunoregulatory effects of physical training in chronic heart failure.

I.	Inhibition of cytokine-chemokine production
II.	Regulation of monocyte activation and adhesion
III.	Reduction of acute phase reactant proteins
IV.	Inhibition of inflammatory cell–growth signals and growth factor production
V.	Reduction of soluble apoptosis signalling molecules
VI.	Reduction of free radical generation
VII.	Attenuation of monocyte-endothelial cell adhesive interaction

regulate peripheral immune responses, resulting in improvement in exercise capacity of CHF patients. Table 2 describes the main immunoregulatory effects of physical training in CHF.

In conclusion, it is tempting to hypothesize that modulation of immunological variables may be useful in the treatment of patients with CHF and that physical training may represent a promising immunomodulatory option possibly intervening in the progression of the syndrome.

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