Expert Perspective

Proinflammatory Cytokines and Peripheral Myopathy in Patients with Chronic Heart Failure: The Beneficial Effect of Physical Exercise

STAMATIS ADAMOPOULOS, JOHN PARISSIS, DIMITRIOS KREMASTINOS

B′ Department of Cardiology, Onassis Cardiac Surgery Center, Athens, Greece

Key words:
Peripheral myopathy, chronic heart failure, proinflammatory cytokines, exercise.

Manuscript received:
February 4, 2004;
Accepted:
June 2, 2004.

Address:
Stamatis Adamopoulos

9, Zinonos St.,
152 34, Halandri,
Athens - Greece
e-mail:
sadamo@bigfoot.com

Chronic heart failure (CHF) is a dynamically evolving syndrome characterised by a multitude of pathophysiological changes that act in parallel with neurohormonal hyperactivity and involve both the centre (cardiac remodelling) and the periphery (endothelial dysfunction and peripheral myopathy).[1] Recent experimental and clinical data have shown that in CHF there are disturbances of peripheral perfusion related to increased peripheral vessel tone, both at rest and after stimulated vasodilation. Moreover, in recent years it has been proved that the skeletal muscles play a role in the pathophysiology of the syndrome, since metabolic and structural changes in the skeletal muscle cells are actively implicated in the deterioration of the clinical symptoms of patients with CHF. Thus, dyspnoea and reduced exercise tolerance, two main symptoms of CHF, appear to develop independently of the haemodynamic changes and the reduction in left ventricular systolic function and are more closely related with the above mentioned disturbances of the peripheral component. Clinical observations have also led to this view, finding a lack of correlation between left ventricular ejection fraction and peak oxygen consumption as an index of exercise capacity in patients with CHF.[2]

Peripheral myopathy and inflammation

A wealth of experimental and clinical observations during the last two decades have focused on the structural and functional abnormalities of the skeletal muscles in CHF, such as atrophy of the muscle fibres, switching of the muscle fibres from oxidant type I to glycolytic type II, the decreased expression of heavy myosine chain type I in skeletal muscle cells, the reduction of mitochondrial enzymes involved in the oxidation of fatty acids and, finally, the reduction in cytochrome C oxidase and mitochondrial volume.[3-5] It is a fact worth noting that many of these skeletal muscle abnormalities cannot be attributed solely to hypo-perfusion of the peripheral tissues, nor to prolonged inactivity on the part of patients with CHF, since physical exercise programmes are encouraged nowadays. An important pathophysiological parameter that appears to play a key role in peripheral myopathy due to CHF is the activation of the proinflammatory cytokine system.[6-8] Although the mechanisms responsible for the abnormal expression of proinflammatory cytokines in the skeletal muscles have not been sufficiently elucidated, it nevertheless appears that the overproduction of free oxygen radicals and the inhibition of anti-oxidative systems (increased oxidative stress) are basic cellular

signals triggering the immuno-inflammatory cascade. In most peripheral tissues oxidative stress activates the nuclear factor NF-κB, which in its turn stimulates the gene transcription of many inflammatory mediators.[9] The increased sympathetic tone and the endothelial dysfunction lead to an inadequate vasodilatory response and promote ischaemia in working skeletal muscles, causing a local increase in oxidative stress and the expression of proinflammatory cytokines.[10]

The pathophysiological link between proinflammatory cytokines and skeletal muscle dysfunction can be confirmed by a study of systematic sepsis, where those inflammatory mediators are responsible to a great degree for the patients' muscular catabolism.[11] Moreover, the administration of the cytokine tumour necrosis factor-alpha (TNF-α) to animals has been seen to cause a reduction in the number of mitochondria and protein reserves in the skeletal muscles, leading to a cachexia phenotype.[12] Proinflammatory cytokines cause muscular wasting through both indirect (e.g. anorexia) and direct (e.g. inhibition of protein synthesis, induction of iNOS) mechanisms. The role of the cytokine-mediated abnormal expression of iNOS in the skeletal muscles has been demonstrated in experimental studies, where the administration of iNOS inhibitors and antioxidants prevented the TNF-α-induced muscle wasting and cachexia.[13] Cytokines such as TNF-α intensify skeletal muscle catabolism by opposing the nutritive action of the anabolic hormone insulin on the skeletal muscle cells or by reducing the expression of growth factors such as IGF-1 in the peripheral tissues.[14,15]

An additional pathophysiological mechanism that is related to the action of proinflammatory cytokines and is responsible for skeletal muscle wasting in CHF is the excessive activation of programmed cell death (apoptosis) in the skeletal muscle cells. In an experimental model of heart failure the levels of circulating TNF-α have been correlated with the number of apoptotic nuclei in peripheral muscle biopsies, and this damaging effect of the cytokine is more exaggerated in rapid response muscle fibres.[16,17] Similarly, muscle biopsies from patients with CHF have shown activation of apoptosis in skeletal muscle cells in around 50% of cases, a phenomenon that is not seen in healthy controls.[18] CHF patients with biopsies positive for skeletal muscle cell apoptosis have a significantly reduced exercise capacity compared with those who have negative biopsies.[18] Moreover, Vescovo et al[19] found that the peak oxygen consumption was inversely correlated with the number of apoptotic nuclei in skeletal muscle cells and with the skeletal muscle mass in patients with CHF.

Table 1. Main pathophysiological mechanisms responsible for peripheral and respiratory muscle dysfunction in chronic heart failure.

- Metabolic/hormonal disturbances of skeletal muscles
  - A) Resistance to the action of anabolic hormones (e.g. insulin, IGF-1).
  - B) Effect of catabolic agents (e.g. TNF-α, IL-6).
  - C) Metabolic mitochondrial abnormalities.
  - D) Over-expression of iNOS – increased oxidative stress.
  - E) Apoptosis of skeletal muscle cells
- Endothelial dysfunction – chronic reduction in skeletal muscle blood flow.
- Prolonged skeletal muscle inactivity.

Apart from structural abnormalities, proinflammatory cytokines also exert a negative effect on skeletal muscle contractility, probably by increasing oxidative stress.[20,21] In experimental models using transgenic technology the over-expression of TNF-α led to a reduction in the contractile strength of the diaphragm with a respective increase in intracellular pH and the intracellular production of free oxygen radicals.[22] This pathological response of the diaphragmatic muscles was to a large degree reversible after the administration of the anti-oxidative agent n-acetylocysteine. In turn, proinflammatory cytokines increase oxidative stress, up-regulating the expression of iNOS in the skeletal muscles and leading to the production of uncontrolled amounts of NO that is converted to toxic hydroxylated derivatives.[23] The toxic derivatives of NO behave as free oxygen radicals, depress the muscles' contractile capability (mainly through reducing the expression of creatinine kinase, an enzyme particularly useful for the transportation of energy from the mitochondria to the cytoplasm), and promote tissue damage and cell death. The main mechanisms responsible for peripheral myopathy in CHF are summarised in Table 1.

The role of physical exercise

Systematic physical exercise is an alternative therapeutic approach that can break the vicious circle of neurohormonal and immuno-inflammatory stimulation of the skeletal and respiratory muscles.[24] Physical exercise – either through a periodic increase in the shear stress of the blood flow or via a reduction

in the activity of depressive factors (e.g. catecholamines) – causes an increase in the expression of the constitutive form of NO synthase (cNOS) while at the same time limiting the production of vasodilatory prostaglandins, reducing the expression of ACE in the vascular wall and blunting oxidative stress and the degradation of NO.[25-27] Even a partial restoration of endothelial function may contribute to the redistribution of blood flow within the skeletal muscles and the selective supply of oxidative muscle fibres, thus accounting for the improvement in the oxidative capacity of the mitochondria and the corresponding increase in exercise capacity resulting from physical exercise programmes in CHF.

Furthermore, Gielen et al[28] showed that a 6-month aerobic exercise programme caused a reduction in the expression of the proinflammatory cytokines TNF-α, IL-6 and IL-1β in peripheral muscle biopsies from CHF patients. This observation is compatible with previous clinical studies, which found that systematic exercise causes an up-regulation of the expression of anti-oxidative enzymes (superoxide dismutase, glutathione system) in the peripheral muscles[29] and a reduction in the levels of a wide spectrum of peripheral markers of inflammation that promote apoptosis and exert a cytotoxic effect on the cardiovascular system.[30,31] More specifically, physical exercise appears to intervene beneficially at various levels of the immunoinflammatory process, as may be deduced from the reduction in the growth factor GM-CSF and the main proinflammatory cytokines TNF-α and IL-6; in the chemotactic cytokine MCP-1, which is a powerful signal for migration of mononuclear leucocytes in the endothelial cells; in the adhesive molecules sICAM-1 and s-VCAM-1, which are overexpressed in activated endothelial cells (as a result of the interaction between monocytes and endothelial cells); in the apoptotic receptor sFas and the apoptosis inducer sFas ligand.

The suppressive effect of physical exercise on the peripheral inflammatory process and the over-expression of proinflammatory cytokines, together with the concomitant increase in exercise capacity, accompanied by a reduction in dyspnoea and a blunting of ventilation disturbances, demonstrate that, by looking beyond conventional haemodynamic strategies and focusing on specialised therapeutic approaches aimed mainly at peripheral muscle catabolism and wasting, we may be able to offer substantial help in the management of patients with CHF. The prolonged improvement in functional capacity and quality of life achieved through physical exercise seems to reflect its beneficial effect on the peripheral component of the syndrome, improving the function of peripheral vessels and skeletal muscles. Table 2 summarises the main mechanisms through which physical exercise leads to an improvement in peripheral myopathy in patients with CHF.

Table 2. Mechanisms of improvement in peripheral muscle function in chronic heart failure after the implementation of physical exercise programmes.

- Improvement in endothelial function (mainly through increased NO production) and peripheral perfusion – increase in capillary density.
- Increase in activity of oxidative enzymes and oxidative mitochondrial metabolism.
- Suppression of premature exhaustion of the mitochondrial energy substrate.
- Blunting of the "muscle ergoreflex" and sympathetic activity.
- Sensitisation to action of anabolic hormones (e.g. insulin, IGF-1).
- Reduction in activity of catabolic agents (proinflammatory cytokines, iNOS-ROS).
- Reduction of skeletal muscle cell apoptosis.

References

1. Mann DL: Mechanisms and models in heart failure: a combinatorial approach. Circulation 1999; 100: 999-1008.
2. Franciosa JA, Park M, Levine TB: Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol 1981; 47: 33-39.
3. Drexler H, Riede U, Munzel T, et al: Alterations of skeletal muscle in chronic heart failure. Circulation 1992; 85: 1751-1759.
4. Mancini DM, Walter G, Reichnek N, et al: Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. Circulation 1992; 85: 1364-1373.
5. Lipkin D, Jones D, Round J, Pool-Wilson P: Abnormalities of skeletal muscle in patients with chronic heart failure. Int J Cardiol 1988; 18: 187-195.
6. Adamopoulos S, Parissis J, Kremastinos D: A glossary of circulating cytokines in chronic heart failure. Eur J Heart Fail 2001; 3: 517-526.
7. Anker SD, Rauchhaus M: Insights into the pathogenesis of chronic heart failure: immune activation and cachexia. Curr Opin Cardiol 1999; 14: 211-216.
8. Gosker HR, Wounters EFM, van der Vusse GJ, Schols AM: Skeletal muscle dysfunction in chronic obstructive pulmonary disease and chronic heart failure: underlying mechanisms and therapy perspectives. Am J Clin Nutr 2000; 71: 1033-1047.
9. Bauerle PA, Baltimore D: NF-kB: ten years after. Cell 1996; 87: 13-20.
10. Li YP, Schwartz RJ, Waddell ID, Holloway BR, Reid MB: Skeletal muscle myocytes undergo protein loss and reactive-

oxygen-mediated NF-kappaB activation in response to tumor necrosis factor alpha. FASEB J 1998; 12: 871-880.
11. Espat NJ, Copeland E, Moldawer LL: Tumor necrosis factor and cachexia: a current perspective. Surg Oncol 1994; 3: 255-262.
12. Tracey KJ, Wei H, Manogue KR, et al: Cachectin/ TNF induces cachexia, anemia and inflammation. J Exp Med 1988; 167: 1211-1227.
13. Buck M, Chojkier M: Muscle wasting and differentiation induced by oxidative stress in a murine model of cachexia is prevented by inhibitors of nitric oxide synthesis and antioxidants. EMBO J 1996; 15: 1753-1765.
14. Patiag D, Gray S, Idris I, Donnelly R: Effects of TNF-α and inhibition of protein kinase C on glucose uptake in L6 myoblasts. Clin Sci (Lond) 2000; 99: 303-307.
15. Meadows KA, Holly JM, Stewart CE: TNF-α-induced apoptosis is associated with suppression of insulin-like growth factor binding protein-5 secretion in differentiating murine skeletal myoblasts. J Cell Physiol 2000; 183: 330-337.
16. Dalla Libera L, Sabbadini R, Renken C, et al: Apoptosis in the skeletal muscle of rats with heart failure is associated with increased serum levels of TNF-alpha and sphingosine. J Mol Cell Cardiol 2001; 33: 1871-1878.
17. Libera LD, Zennaro R, Sandri M, Ambrosio GB, Vescovo G: Apoptosis and atrophy in rat slow skeletal muscles in chronic heart failure. Am J Physiol 1999; 277: C982-986.
18. Adams V, Jiang H, Yu J, et al: Apoptosis in skeletal myocytes of patients with chronic heat failure is associated with exercise intolerance. J Am Coll Cardiol 1999; 33: 959-965.
19. Vescovo G, Volterrani M, Zennaro R, et al: Apoptosis in the skeletal muscle of patients with heart failure: investigation of clinical and biochemical changes. Heart 2000; 84: 431-437.
20. Reid MB, Li YP: Cytokines and oxidative signalling in skeletal muscle. Acta Physiol Scand 2001; 171: 225-232.
21. Parissis J, Filippatos G, Nikolaou V, Adamopoulos S: Cytokines and anti-cytokine therapeutic approaches in chronic heart failure. Eur J Intern Med 2002; 13: 356-364.
22. Wilcox PG, Wakai Y, Walley KR, Cooper DJ, Road J: TNF-α decreases in vivo diaphragm contractility in dogs. Am J Respir Crit Care Med 1994; 150: 1368-1373.
23. Hambrecht R, Adams V, Gielen S, et al: Exercise intolerance in patients with chronic heart failure and increased expression of inducible nitric oxide synthase in the skeletal muscle. J Am Coll Cardiol 1999; 33: 174-179.
24. Adamopoulos S, Parissis J, Kremastinos D: New aspects for the role of physical training in the management of patients with chronic heart failure. Int J Cardiol 2003; 90: 1-14.
25. Inone N, Ramascamy S, Fukai T, Nereri RM, Harrison DG: Shear stress modulates expression of Cu/Zn superoxide dismutase in human aortic endothelial cells. Circ Res 1996; 79: 32-37.
26. Holler A, Huyand A, Sun D, Kaley G: Exercise training augments flow-dependent dilation in rat skeletal muscle arterioles: role of endothelial nitric oxide and prostaglandins. Circ Res. 1995; 76: 544-550.
27. Hambrecht R, Fiehn E, Weigl C, et al: Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. Circulation 1998; 98: 2709-2715.
28. Gielen S, Adams V, Mobius-Winkler S, et al: Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. J Am Coll Cardiol 2003; 42: 861-868.
29. Ennezat PV, Malendowicz SL, Testa M, et al: Physical training in patients with chronic heart failure enhances the expression of genes encoding antioxidative enzymes. J Am Coll Cardiol 2001; 38: 194-198.
30. Adamopoulos S, Parissis J, Karatzas D, et al: Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fas Ligand system in patients with chronic heart failure. J Am Coll Cardiol 2002; 29: 653-663.
31. Adamopoulos S, Parissis J, Kroupis C, et al: Physical training reduces peripheral markers of inflammation in patients with chronic heart failure. Eur Heart J 2001; 22: 791-797.