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Research Article

Effect of Exercise Training on Interleukin-6, Tumour Necrosis Factor Alpha and Functional Capacity in Heart Failure

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Background. We pooled data from four studies, to establish whether exercise training programs were able to modulate systemic cytokine levels of tumour necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6). A second aim was to establish if differences in ExT regimens are related to degree of change in cytokines and peak VO_2. *Methods*. Data from four centres relating to training protocol, exercise capacity, and cytokine measures (TNF-alpha and IL-6) were pooled for analysis. *Results*. Data for 106 CHF patients were collated (98 men, age 62 ± 10 yrs, wt 79 ± 14 Kg). Patients were moderately impaired (peak VO_2 16.9 ± 4.4 mls/kg/min), with moderate LV systolic dysfunction (EF $30 \pm 6.9\%$), 78% (83) had ischaemic cardiomyopathy. After ExT, peak VO_2 increased 1.4 ± 3.4 ml/kg/min ($P < .001$), serum TNF-alpha decreased 1.9 ± 8.6 pg/ml ($P = .02$) and IL-6 was not significantly changed (0.5 ± 5.4 pg/ml, $P = .32$) for the whole group. Baseline and post-training peak VO_2 changes were not correlated with change in cytokine levels. *Conclusions*. Exercise training reduces levels TNF-alpha but not IL-6 in CHF. However, across a heterogenic patient group, change in peak VO_2 was not correlated with alterations in cytokine levels. While greater exercise volume (hours) was superior in improving peak VO_2, no particular characteristic of ExT regimes appeared superior in effecting change in serum cytokines.

1. Introduction

Inflammatory activation with increased serum cytokine levels has been described by several authors as an important factor in the progression of the syndrome of chronic heart failure (CHF) [1–3]. In multifactorial analyses, elevated levels of tumour necrosis factor-(TNF-) alpha and interleukin-(IL-) 6 have been identified as prognostic heart failure markers [4–6]. Cytokines act as catabolic factors involved in the pathogenesis of muscle wasting and cardiac cachexia [3, 7], and increased levels of serum TNF-alpha have been identified in patients with reduced skeletal muscle cross-sectional area and peripheral muscle strength [1]. There also exists a statistical significant association between elevated serum cytokine levels (especially TNF-alpha) and New York Heart Association (NYHA) functional class as well as exercise intolerance [2]. Inflammatory cytokines may alter skeletal muscle histology and have a negative impact on left ventricular remodelling and cardiac contractility [2, 3, 8]. The inflammatory response is also associated with progression of atherosclerosis [9], oxidative stress [10], NO impairment [11], vasoconstriction, endothelial cell apoptosis [12], and adverse vascular remodelling [13].

Exercise training has been documented to improve the inflammatory profile in CHF by inhibition of cytokine-chemokine production, regulation of monocyte activation and adhesion, inhibition of inflammatory cell-growth signals and growth factor production, reduction of soluble apoptosis signalling molecules [12], and attenuation of monocyte-endothelial cell adhesive interaction [14]. A study of 277 patients with coronary artery disease reported a significant 41% reduction in high-sensitivity C-reactive protein following exercise training [15]. A recent study of four-month duration, utilizing combined endurance/resistance

Table 1: Studies identified in PUBMED, MEDLINE search.

Study	Subjects(Control)	Year	Cytokines measured	% △ VO_2	Mode of Exercise
Adamapoulos et al. [23]	12	2001	Soluble adhesion molecules	13	Home bike
Adamopoulos et al. [12]	24	2002	TNF-alpha, Interleukin-6	15	Home bike
Conraads et al. [16]	23 (12)	2002	TNF-alpha, Interleukin-6	7.5	Bike and resistance training
Ferraz et al. [21]#	30 (10)	2004	TNF-alpha, Interleukin-6	23	Bike
Gielen et al. [2]	20 (10)	2003	TNF-alpha, Interleukin-1, 6 and beta In both serum and skeletal muscle	29	Bike
Karavidas et al. [24]	16 (8)	2006	TNF-alpha, Interleukin-6, 10	7.5*	Electrical stimulation
Larsen et al. [22]#	28	2001	TNF-alpha, Interleukin-6,8	8*	Aerobic endurance training and home bike
Larsen et al. [25]	25	2008	Plasma Chromogranin A (CgA)	8*	Aerobic endurance training and home bike
Laoutaris et al. [26]	38	2007	TNF-alpha, Interleukin-6	12	Low versus high intensity inspiratory muscle training
LeMaitre et al. [17]#	46	2004	TNF-alpha, Interleukin-6	3	Bike and electrical stimulation
Niebauer et al. [27]	18 (9)	2005	TNF-alpha Interleukin-6, e-selectin	11	Bike
Smart [28]#	22	2008	TNF-alpha, Interleukin-6, brain natriurietic peptide (BNP)	20	Bike
Xu et al. [18]	60 (28)	2002	TNF-alpha	Unknown	Unknown

* % change in 6-minute walk distance (Peak VO_2 not measured). #Study used in this paper.

training demonstrated reduced TNF-alpha receptor levels (TNFR1 and TNFR2) and a significant (7.5%) increase in peak VO_2 in patients with ischemic cardiomyopathy, although changes in IL-6 and TNF-alpha were not apparent [16]. This effect on circulating levels of TNF-alpha receptors is also reported after 6 weeks of cycle ergometry [17]. In this study, there were no alterations in IL-6, C-reactive protein (CRP), or TNF-alpha. In addition, electrical muscle stimulation provided no changes in any of the aforementioned cytokines. Larsen et al. [8] reported an 11% increase in peak VO_2 following 3 months of endurance training; TNF-alpha was significantly reduced, and this decrease was significantly correlated to the increase in peak VO_2. Adamopoulos [14] reported a 13% increase in functional capacity with a 12-week cycle ergometry training program, which correlated with lower levels of soluble adhesion molecules. The authors later reported a strong and highly significant correlation between improvements in peak VO_2 (15%) and reduction in TNF-alpha, soluble TNFR-1 and -2, and IL-6 [12]. Plasma TNF-alpha is also documented to decrease after twice daily 6-minute walk tests in NYHA II/III heart failure patients [18]. A recently published study reported absent von Willebrand factor (vWF) release upon exercise testing in heart failure patients; this normalised following 6 months of exercise training; other plasma endothelial markers were unaltered [19].

Changes in skeletal muscle, but not systemic expression of TNF-alpha, IL-1-beta, and IL-6 have been reported in heart failure patients undertaking a regimen of 10 minutes cycling, 4–6 times daily for 6 months [2]. This exercise program resulted in large changes in functional capacity (29%), nearly twice the mean expected increment (17%) shown from our review of 81 heart failure exercise training studies [20]. This study suggested the existence of a cytokine cascade where levels may be changed at altered rates in different tissues. As heart failure exercise training studies are often small, we sought by pooling data from four studies to establish whether exercise training programs were able to modulate systemic cytokine levels. A second aim was to establish if differences in ExT regimens are related to the degree of change in cytokines and peak VO_2.

2. Methods

We searched PUBMED and MEDLINE for exercise training studies in heart failure patients that had measured one or more of the proinflammatory cytokines. The full list of studies is summarized in Table 1. The focus of this work was interleukin-6 and TNF-alpha as these cytokines were measured in 10 exercise training studies, the correspondence authors of which were contacted for their cooperation in collaboration. Authors were requested to provide individual patient data from their study; four centres provided data (Table 2). One study was a conference proceedings abstract [21]. Sufficient data were not available to analyse changes in other cytokines.

Table 2: Clinical characteristics and pharmacotherapy of the 106 patients.

Clinical characteristics	
Age (Years)	61.8 ± 9.9
Male (%)	98 (92.5)
Body mass (kg)	78.7 ± 13.7
Peak VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	16.9 ± 4.4
Diabetes (%)	11 (10)
Previous myocardial infarction (%)	86 (81)
Atrial fibrillation (%)	27 (26)
NYHA class II/III	49/57
LVEF (%)	30 ± 6.9
Medications	
Beta-blocker (%)	44 (42)
ACE-inhibitor/antagonist (%)	95 (90)
Digoxin (%)	67 (63)
Nitrates (%)	40 (38)

2.1. Blood Sampling and Analysis. In 3 studies, plasma or serum samples were obtained by venipuncture (arterial cannula used in Larsen's study) and stored on ice. In all studies, venipuncture collections were taken between 0900, and 1200, at least 24 hours and not more than 5 days after the last exercise session, thus negating the effects of the intervention. Within one hour, samples were centrifuged at 4°C, 1500–2000 RPM for 10 minutes, and then separated into aliquots and stored at between −75°C and −80°C. Concentrations of IL-6 or TNF-alpha were measured by commercially available enzyme-linked immunosorbent assays (ELISAs) (R&D systems Minneapolis, Minnesota) in all 4 studies. The intra- and interassay coefficients of variation were <10% for all assays. In one study, 16 healthy, male volunteers of approximately the same age (62 ± 5 years) served as controls [22] although this data was not included in our analyses.

2.2. Metabolic Exercise Testing and Exercise Training. All four collaborating investigators completed baseline and posttraining metabolic exercise tests to establish functional capacity.

Larsen and Smart used cycle ergometers with a 15 W and 10 W per min stepped protocol, respectively; LeMaitre and Ferraz used a modified Bruce treadmill protocol.

One study used a regime of supervised aerobic exercise training 3 times per week. Two studies used supervised cycle ergometry as the primary mode of exercise training [21, 22], and one study used both home-based and neuromuscular stimulation of the legs [17].

2.3. Data Extraction. Mode of training, program duration and exercise intensity were examined. Baseline and post-training cytokine levels, peak VO_2, left ventricular ejection fraction (LVEF), clinical, demographic, and pharmacological characteristics of patients are shown in Table 2.

Table 3: Exercise program parameters and change in primary outcome measures in the 4 studies.

	Ferraz	Larsen	LeMaitre	Smart
Weeks	24	12	6	16
Minutes/Wk	135	90	150	90
Freq. sessions/Wk	3	3	5	3
Intensity (% max)	67	80	70	70
Total hours	54	54	15	48

2.4. Statistical Analysis. Paired student t-tests were used to analyse baseline and postintervention changes in cytokines and peak VO_2. ANOVA (2×4) was used to analyse differences between the four datasets. Pearson correlation coefficients were established for change in cytokines and peak VO_2. Univariate and multivariate regression analysis with change in TNF-alpha as the dependent variable were used to determine factors leading to cytokine change. Data are expressed as mean +/− standard deviation unless otherwise stated. Significance was accepted at the 5% level ($P < .05$).

3. Results

3.1. Baseline Measures. The four collaborating authors provided data on 106 patients (98 male, age 62 ± 10 yrs, body weight 79 ± 14 Kg). Patients were moderately impaired (peak VO_2 16.9 ± 4.4 mls/kg/min), with moderate LV systolic dysfunction (EF 30 ± 6.9%). Seventy eight % (83) had an ischaemic cardiomyopathy (Table 2). Adherence data relating to training regimes were 87.2 ± 1.9% [21] and 85 ± 12% [28] and were unavailable for the other 2 studies.

3.2. Training Regimes. Regimes varied between 3 and 5 exercise sessions per week, at an intensity of 58–80% of peak VO_2. Program durations were between 6 and 24 weeks, 90–150 minutes per week, and total program hours varied between 15 and 54 hours (Table 3).

3.3. Pooled Posttraining Changes. After training, peak VO_2 increased by 1.4 ± 3.4 mL/kg/min or 9% ($P < .001$) from 16.9 ± 4.4 to 18.4 ± 4.5, serum TNF-alpha decreased from a baseline value of 13 ± 15.2 pg/mL by 1.9 ± 8.6 pg/mL ($P = .02$), and IL-6 increased slightly from a baseline value of 7.8 ± 11.4 pg/mL by 0.5 ± 5.4 pg/mL ($P = .32$). Cytokine changes for each study can be seen in Figure 1. Body weight was unchanged following exercise training. None of the clinical, demographic, or pharmacologic variables were correlated with changes in circulating IL-6 or TNF-alpha following training. The correlations between change in posttraining peak VO_2 and changes in TNF-alpha ($r = 0.023$, $P = .82$) and IL-6 ($r = -0.12$, $P = .21$) were not significant. Change in TNF-alpha was correlated with exercise session duration and anerobic threshold (both $r = 0.21$, $P = .31$), univariate but not multivariate analysis identified that previous myocardial infarction, longer exercise session duration, and higher body mass index predicted change in TNF-alpha ($r^2 = 0.18$, $P = .001$).

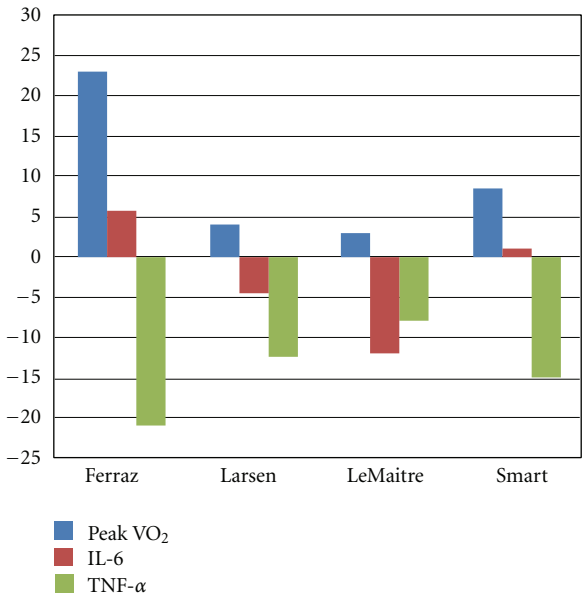

Figure 1: Change in cytokines and peak VO_2 across the four studies.

3.4. Optimal Exercise Program Components for Peak VO_2 and Cytokine Changes. A total exercise program duration of 54 hours appeared to be superior than 15 or 18 hours in effecting change in peak VO_2 ($P < .001$); however, no difference was seen for change in cytokine levels. The longest program duration resulted in a greater increment in peak VO_2 compared to 12 weeks ($P = .003$) and 6 weeks ($P = .001$), while peak VO_2 or 6-minute walk distance was unchanged in the ExT programs of 6 and 12 weeks duration.

4. Discussion

Pooled data from four studies demonstrated that alterations in levels of the cytokines IL-6 and TNF-alpha are not necessarily uniform. Increments in peak VO_2 following exercise training are widely accepted; however, they may be unrelated to changes in cytokine levels. Moreover, changes in particular cytokines appear to be independent of one another. One cannot be sure about the variable effects of the different program parameters and exercise adherence rates; nevertheless, the mean change in functional capacity from the four studies was 8%, suggesting that cumulatively the four exercise programs provided stimulus for a possible favourable change in cytokine expression. Interpretation of this pooled data is limited by the fact that several other centres did not supply data. Table 2 suggests that study participants showed heterogeneity for age, peak, VO_2 and beta-blocker use.

4.1. Expectations of Favourable Changes in Cytokine Expression. Moderate endurance activity in frail, elderly, but otherwise healthy persons has previously been reported to influence circulating cytokine levels [29]. As our patients had mild to moderate heart failure, it is not surprising to observe that levels of systemic TNF-alpha were decreased after training, thereby initiating anti-inflammatory effects. The finding that IL-6 was unchanged after training is more puzzling. However, one study has suggested that IL-6 produced by exercising muscle is thought to exert an anti-inflammatory effect [30]. These data suggest that production and removal of TNF-alpha and IL-6 may be, at least partially, from independent mechanisms and may have opposing effects (inflammatory versus anti-inflammatory). Recent clinical trials have not shown benefit from treatments that target TNF-alpha. A clinical trial of etanercept (a TNF-alpha antagonist) therapy has cast doubt on the role of cytokines in the pathogenesis of heart failure [31]. There are then implications for health professionals or researchers in the process of designing an exercise program for heart failure patients. Primary end points of CHF exercise programs should perhaps not include lowering cytokine levels as they may represent surrogate markers of efficacy; this may be particularly true in patients with milder degrees of CHF. In this population, program design may be better focussed on the parameters such as program frequency (sessions/week), duration (number of weeks), and intensity that may have a greater effect on peak VO_2 changes. Peak VO_2 improvement from exercise training may be linked to attenuated levels of oxidative stress which in turn may attenuate cytokine expression. Previous work in healthy older adults [32] and heart failure patients [33] has shown intermittent exercise programs to be at least more effective in improving peak VO_2 than a continuous regime that would produce greater cumulative oxidative stress. In our work, peak VO_2 was not significantly changed in patients who exercised despite utilizing a reasonable volume of exercise to elicit functional capacity changes.

In heart failure, the effect of inflammation, which may be due partly to inactivity, may manifest in the terminal disease phase. The study by Adamopoulos et al. [14] may provide the best evidence to date linking change in peak VO_2 and cytokines in heart failure patients. The small cytokine change shown in our studies may be due to the fact that our patients exhibited mild to moderate heart failure symptoms. The participants in the study of Adamopoulos et al. [14] exhibited moderate to severe symptoms. In addition, our participants had higher left ventricular ejection fractions (30% versus 24%) than those of Adamopoulos et al. [14]. Exercise training has been shown to significantly reduce the local muscle expression of TNF-alpha, IL-1-beta, IL-6, and iNOS in the skeletal muscle of CHF patients [8]. In turn, physical exercise has been shown to improve both basal endothelial nitric oxide (NO) formation and agonist-mediated endothelium-dependent vasodilation of the skeletal muscle vasculature in patients with CHF. The correction of endothelium dysfunction is associated with a significant increase in exercise capacity [34]. These local anti-inflammatory and systemic effects of exercise may attenuate the catabolic wasting process associated with CHF progression [3]. In addition to an overall beneficial effect on exercise capacity, combined endurance/resistance exercise training has an anti-inflammatory effect in patients with heart disease [16]. These skeletal muscle and anti-inflammatory changes may explain why alterations in TNF-alpha levels are most likely to be observed in patients with moderate or severe heart failure.

4.2. Conclusions. Exercise training reduces levels of TNF-alpha but not IL-6 in CHF. However, across a heterogenic patient group, change in peak VO_2 was not correlated with alterations in cytokine levels. While greater exercise volume (number of hours) was superior in improving peak VO_2, no particular characteristic of ExT regimes appeared superior in effecting change in serum cytokines.

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References

[1] J. Niebauer, "Inflammatory mediators in heart failure," *International Journal of Cardiology*, vol. 72, no. 3, pp. 209–213, 2000.

[2] S. Gielen, V. Adams, S. Möbius-Winkler et al., "Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 42, no. 5, pp. 861–868, 2003.

[3] S. D. Anker and S. Von Haehling, "Inflammatory mediators in chronic heart failure: an overview," *Heart*, vol. 90, no. 4, pp. 464–470, 2004.

[4] J. Orús, E. Roig, F. Perez-Villa et al., "Prognostic value of serum cytokines in patients with congestive heart failure," *Journal of Heart and Lung Transplantation*, vol. 19, no. 5, pp. 419–425, 2000.

[5] M. Rauchhaus, W. Doehner, D. P. Francis et al., "Plasma cytokine parameters and mortality in patients with chronic heart failure," *Circulation*, vol. 102, no. 25, pp. 3060–3067, 2000.

[6] A. Deswal, N. J. Petersen, A. M. Feldman, J. B. Young, B. G. White, and D. L. Mann, "Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone Trial (VEST)," *Circulation*, vol. 103, no. 16, pp. 2055–2059, 2001.

[7] S. D. Anker, W. Steinborn, and S. Strassburg, "Cardiac cachexia," *Annals of Medicine*, vol. 36, no. 7, pp. 518–529, 2004.

[8] A. I. Larsen, S. Lindal, P. Aukrust, I. Toft, T. Aarsland, and K. Dickstein, "Effect of exercise training on skeletal muscle fibre characteristics in men with chronic heart failure. Correlation between skeletal muscle alterations, cytokines and exercise capacity," *International Journal of Cardiology*, vol. 83, no. 1, pp. 25–32, 2002.

[9] D. Tousoulis, M. Charakida, and C. Stefanadis, "Inflammation and endothelial dysfunction as therapeutic targets in patients with heart failure," *International Journal of Cardiology*, vol. 100, no. 3, pp. 347–353, 2005.

[10] S. Ichihara, Y. Yamada, G. Ichihara et al., "Attenuation of oxidative stress and cardiac dysfunction by bisoprolol in an animal model of dilated cardiomyopathy," *Biochemical and Biophysical Research Communications*, vol. 350, no. 1, pp. 105–113, 2006.

[11] O. Parodi, R. De Maria, and E. Roubina, "Redox state, oxidative stress and endothelial dysfunction in heart failure: the puzzle of nitrate-thiol interaction," *Journal of Cardiovascular Medicine*, vol. 8, no. 10, pp. 765–774, 2007.

[12] S. Adamopoulos, J. Parissis, D. Karatzas et al., "Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fas ligand system in patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 39, no. 4, pp. 653–663, 2002.

[13] S. Adamopoulos, J. T. Parissis, and D. T. Kremastinos, "New aspects for the role of physical training in the management of patients with chronic heart failure," *International Journal of Cardiology*, vol. 90, no. 1, pp. 1–14, 2003.

[14] S. Adamopoulos, J. Parissis, C. Kroupis et al., "Physical training reduces peripheral markers of inflammation in patients with chronic heart failure," *European Heart Journal*, vol. 22, no. 9, pp. 791–797, 2001.

[15] R. V. Milani, C. J. Lavie, and M. R. Mehra, "Reduction in C-reactive protein through cardiac rehabilitation and exercise training," *Journal of the American College of Cardiology*, vol. 43, no. 6, pp. 1056–1061, 2004.

[16] V. M. Conraads, P. Beckers, J. Bosmans et al., "Combined endurance/resistance training reduces plasma TNF-α receptor levels in patients with chronic heart failure and coronary artery disease," *European Heart Journal*, vol. 23, no. 23, pp. 1854–1860, 2002.

[17] J. P. LeMaitre, S. Harris, K. A. A. Fox, and M. Denvir, "Change in circulating cytokines after 2 forms of exercise training in chronic stable heart failure," *American Heart Journal*, vol. 147, no. 1, pp. 100–105, 2004.

[18] D. Xu, B. Wang, Y. Hou, H. Hui, S. Meng, and Y. Liu, "The effects of exercise training on plasma tumor necrosis factor-alpha, blood leucocyte and its components in congestive heart failure patients," *Zhonghua Nei Ke Za Zhi*, vol. 41, no. 4, pp. 237–240, 2002.

[19] L. W. E. Sabelis, P. J. Senden, R. Fijnheer et al., "Endothelial markers in chronic heart failure: training normalizes exercise-induced vWF release," *European Journal of Clinical Investigation*, vol. 34, no. 9, pp. 583–589, 2004.

[20] N. Smart and T. H. Marwick, "Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity," *American Journal of Medicine*, vol. 116, no. 10, pp. 693–706, 2004.

[21] A. Ferraz, E. A. Boochi, R. S. Meneghelo, I. I. Umeda, and N. Salvarane, "High sensitive C-reactive protein is reduced by exercise training in chronic heart failure patients: a prospective, randomized, controlled study," *Circulation*, vol. 110, pp. 793–794, 2004.

[22] A. I. Larsen, P. Aukrust, T. Aarsland, and K. Dickstein, "Effect of aerobic exercise training on plasma levels of tumor necrosis factor alpha in patients with heart failure," *American Journal of Cardiology*, vol. 88, no. 7, pp. 805–808, 2001.

[23] S. Adamopoulos, A. J. Coats, F. Brunotte et al., "Physical training improves skeletal muscle metabolism in patients with chronic heart failure," *Journal of the American College of Cardiology*, vol. 21, no. 5, pp. 1101–1106, 1993.

[24] A. I. Karavidas, K. G. Raisakis, J. T. Parissis et al., "Functional electrical stimulation improves endothelial function and reduces peripheral immune responses in patients with chronic heart failure," *European Journal of Cardiovascular Prevention and Rehabilitation*, vol. 13, no. 4, pp. 592–597, 2006.

[25] A. I. Larsen, K. B. Helle, M. Christensen, J. T. Kvaloy, T. Aarsland, and K. Dickstein, "Effect of exercise training on chromogranin A and relationship to N-ANP and inflammatory cytokines in patients with chronic heart failure," *International Journal of Cardiology*, vol. 127, no. 1, pp. 117–120, 2008.

[26] I. D. Laoutaris, A. Dritsas, M. D. Brown et al., "Immune response to inspiratory muscle training in patients with chronic heart failure," *European Journal of Cardiovascular Prevention and Rehabilitation*, vol. 14, no. 5, pp. 679–685, 2007.

[27] J. Niebauer, A. L. Clark, k. M. Webb-Peploe, and A. J. Coats, "Exercise training in chronic heart failure: effects on pro-inflammatory markers," *European Journal of Heart Failure*, vol. 7, no. 2, pp. 189–193, 2005.

[28] N. Smart, "Effects of exercise training on functional capacity, quality of life, cytokine and brain natriuretic peptide levels in hart failure patients," *Journal of Medical and Biological Sciences*, vol. 2, no. 1, 2008.

[29] J. S. Greiwe, B. Cheng, D. C. Rubin, K. E. Yarasheski, and C. F. Semenkovich, "Resistance exercise decreases skeletal muscle tumor necrosis factor α in frail elderly humans," *FASEB Journal*, vol. 15, no. 2, pp. 475–482, 2001.

[30] A. M. W. Petersen and B. K. Pedersen, "The anti-inflammatory effect of exercise," *Journal of Applied Physiology*, vol. 98, no. 4, pp. 1154–1162, 2005.

[31] D. L. Mann, J. J. V. McMurray, M. Packer et al., "Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL)," *Circulation*, vol. 109, no. 13, pp. 1594–1602, 2004.

[32] N. Morris, G. Gass, M. Thompson, G. Bennett, D. Basic, and H. Morton, "Rate and amplitude of adaptation to intermittent and continuous exercise in older men," *Medicine and Science in Sports and Exercise*, vol. 34, no. 3, pp. 471–477, 2002.

[33] K. Meyer, L. Samek, M. Schwaibold et al., "Interval training in patients with severe chronic heart failure: analysis and recommendations for exercise procedures," *Medicine and Science in Sports and Exercise*, vol. 29, no. 3, pp. 306–312, 1997.

[34] R. Hambrecht, E. Fiehn, C. Weigl et al., "Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure," *Circulation*, vol. 98, no. 24, pp. 2709–2715, 1998.