Beneficial Effects of Exercise Training in Patients with Chronic Heart Failure

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Abstract: Several human and experimental studies have been performed to show the effects of exercise training on chronic heart failure (CHF). These studies have shown that exercise improves the adverse pathophysiologic changes which occur with CHF, including enhanced exercise capacity, ventilation, skeletal muscle metabolism, cardiac function, quality of life, and peripheral blood flow. In addition, there is an improved modulation of inflammatory, autonomic, and hormonal dysregulation after exercise training. This review focuses on the current evidence surrounding the beneficial effects of exercise training in CHF patients.

Keywords: Heart Failure, exercise training, functional capacity.

INTRODUCTION

Several therapeutic regimens have emerged for chronic heart failure (CHF), a progressively debilitating disease caused by inadequate cardiac performance. Exercise training, one of the currently few well known therapeutic modalities, was considered contraindicated in the 1970s. There are old studies in favor of prolonged bed rest to avoid worsening of the clinical conditions in CHF patients [1]. In late 1980s and early 1990s the first promising effects of exercise training on CHF patients were reported and subsequently a new era in CHF treatment using exercise training as a modality begun [2, 3].

In the past two decades several randomized controlled trials and experimental studies have been conducted to assess various favorable effects of exercise training on CHF and mechanisms of these effects. In this review, we will briefly describe pathophysiologic changes in CHF followed by the effects of exercise training on these abnormalities.

EXERCISE TRAINING (ET) & EXERCISE CAPACITY

One of the cardinal symptoms of CHF is exercise intolerance that is closely correlated with the severity of the pathology. The reduction in exercise tolerance in CHF is caused by impairments in cardiac, peripheral vascular, pulmonary, and respiratory as well as skeletal muscle function [4-26].

Several studies have demonstrated an improvement in exercise capacity (Table **1**) as assessed by exercise duration and walking distance (6-minute walk), achieved METs, and most importantly Peak VO2 [27-57]. Peak VO2 or VO2 max is one of the best indicators of cardiovascular fitness and aerobic capacity (exercise capacity) in CHF patients. It is also a strong measurement of prognosis in this patient population [58]. The mean increase in Peak VO2 in these studies has ranged from 4% [59] to 31% [32]. In a systemic review by Smart *et al.* [57], the mean increase in peak VO2 was 17%, 15%, 9%, and 16% in 40 studies of aerobic training, 13 studies of combined strength and aerobic training, 3 studies of strength training, and one study of inspiratory training in CHF patients, respectively.

Table 1: Effects of Exercise Training on Exercise Capacity in CHF Patients

	Exercise training effects
Peak VO2	Increase
Mean walking distance	Increase
Exercise duration	Increase
Mean METs achieved during exercise	Increase

VO2: Oxygen consumption or uptake; METs: Metabolic equivalents.

Improvements in Peak VO2 have been reported to be independent of the exercise type, which may include aerobic, strength, combined aerobic and strength, or of inspiratory training [57, 175]. The improvement in Peak VO2 has been shown to be less among patients with ischemic vs. patients with non-ischemic cardiomyopathy [28]. Exercise training has been demonstrated to increase mean walking distance as measured by the 6-minute walk [32, 61-64], exercise duration [28, 61, 62, 64-67], and mean METs achieved during exercise test [62].

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There is also a significant association between improvements in the Kansas City Cardiomyopathy Questionnaire's (KCCQ) overall summary score, which measures a patient-reported health status and improvements in exercise duration (r=0.28; P<0.001), peak VO2 (r = 0.21; P<0.001), and 6-minute walk distance (r = 0.18; P<0.001) after 12 months of exercise training according to HF-ACTION study [68].

ET & VENTILATION

Pulmonary function is reduced in CHF patients. Respiratory muscle endurance decreases due to generalized skeletal muscle myopathy [69] and pulmonary diffusion capacity reduces [4, 5] as a result of an overall decrease in lung perfusion [6] and alveolar-capillary membrane conductance [7].

However, with exercise, the muscle fibers of the diaphragm shift from fast to slow and the diaphragm's oxidative capacity increases while its glycolytic capacity decreases, which mimics the changes that occur in skeletal muscle caused by endurance exercise [8]. Chronic hyperventilation caused by ventilation/ perfusion mismatch [9], and minute ventilation dramatically increases in proportion to the increased carbon dioxide production that occur when the patient exercises [9, 10].

Exercise training in CHF improves pulmonary function (Table **2**) in different ways. It increases peak (maximum) ventilation [28, 47, 70] as well as many other parameters [70]. The improvement of these parameters eventually leads to a decrease in VE/VCO2 slope and more efficient ventilation [70-74]. This reduction in VE/VCO2 slope means that the patients with CHF tend to breathe less at any given workload.

Table 2: Effects of Exercise Training on Pulmonary Function in CHF Patients

	Exercise training effects
Peak ventilation	Increase
Carbondioxide production	Increase
VE/VCO2 slope	Decrease
Oxygen uptake efficiency slope	Increase
Anaerobic threshold	Increase
Lung diffusion capacity	Increase
Alveolar-capillary conductance	Increase
Pulmonary capillary blood volume	Increase
Pulmonary arteriolar resistance	Decrease

VE: Ventilation; VCO2: Carbon dioxide production.

This slope has been demonstrated to be a powerful significant prognostic measure of mortality in two years in CHF patients [75].

Gademan *et al.* [72], used Oxygen Uptake Efficiency Slope (OUES) as a novel measure of cardiopulmonary reserve. (OUES is independent of peak exercise load when compared to peak VO2 and VE/VCO2). OUES is significantly (P<0.001) improved after exercise training in CHF patients. Further studies are needed to demonstrate the prognostic value of OUES in this population. Exercise training also delays the anaerobic threshold in CHF patients [47, 70, 73, 76-78]. Guazzi *et al.* [74] showed that exercise training improves pulmonary function by increasing lung diffusion capacity, conductance of alveolar-capillary, pulmonary capillary blood volume, and decreasing the pulmonary arteriolar resistance. The improved pulmonary function may contribute to more efficient ventilation and improved exercise performance in CHF patients.

ET & CARDIAC FUNCTION

As mentioned before, a reduced capacity to perform aerobic exercise is a hallmark of CHF and seems to be under influence of several factors, especially reduced blood flow to skeletal muscles during exercise due to impairment in cardiac output and other aforementioned abnormalities [23, 79]. Compared to healthy individuals, CHF patients may achieve less than half of the maximal attainable cardiac output at peak exercise level. Patients with CHF have an already reduced stroke volume that only rises modestly up to 50 to 65 percent of the stroke volume of the healthy subjects during exercise. A reduced stroke volume along with a lower maximal achievable heart rate at peak exercise in these patients are the main factors behind a reduced cardiac output [79]. Impaired left ventricular (LV) systolic function and a reduced preload reserve decreases the ability of the already dilated LV to increase End Diastolic Volume (EDV). In addition, a decreased chronotropic reserve reduces the degree of increase in heart rate above the resting level, because of an already elevated heart rate at rest and lower attainable maximum heart rate at peak exercise level [79, 80]. The reduction in heart rate immediately after exercise (heart rate recovery), which is considered to be an indicator of parasympathetic nervous system tone, is also reduced in CHF patients.

Exercise training has been shown to improve cardiac performance (Table **3**) in CHF patients. [47].

Experimental studies have demonstrated that exercise training enhances the cardiac function by restoring the contractility of cardiomyocytes and increasing their sensitivity to calcium [81-84]. Recent meta-analysis by Haykowsky *et al.* showed that exercise training had favorable effects on left ventricular systolic function [85]. They reported a significant enhancement of left ventricular ejection fraction (LVEF), a significant decrease in both EDV and end systolic volume (ESV), and a reversal in LV remodeling after aerobic exercise training in clinically stable CHF patients. Their study also showed that the beneficial effects of aerobic exercise training were not confined to aerobic and strength training or isolated strength training alone. Another meta-analysis by Van Tol *et al.* [86], showed a significant increase in cardiac output, maximal heart rate, and systolic blood pressure (SBP) after exercise training in patients with CHF. Exercise training leads to a decrease in heart rate at rest and to increases in both the chronotropic reserve and heart rate recovery [54, 87], particularly *via* a beneficial effect on the sympathetic nervous system. These changes are also observed in patients receiving a beta-blocker [54, 88].

Table 3: Effects of Exercise Training on Cardiac Function in CHF Patients

	Exercise training effects
Contractility of cardiomyocytes	Increase
Cardiomyocytes sensitivity to calcium	Increase
Left ventricular systolic function	Improve
Left ventricular diastolic function	Improve
Left ventricle remodeling	Decrease
Cardiac output	Increase
Maximal heart rate	Increase
Systolic blood pressure	Increase
Heart rate at rest	Decrease
Chronotropic reserve	Increase
Heart rate recovery	Increase

Studies have shown that exercise training may also improve cardiac diastolic function. Exercise training lowers the LV diastolic wall stress [89], it increases peak early left ventricular diastolic filling rate [90], improves left ventricular diastolic stiffness [91], and reduces LV filling pressure [52].

ET & SKELETAL MUSCLE

Apart from pulmonary skeletal muscles, peripheral skeletal muscles are also influenced by CHF. CHF patients suffer from skeletal muscle myopathy and reduced muscle power, strength, and endurance [92]. In CHF patients, glycolytic metabolism (anaerobic metabolism) increases and oxidative phosphorylation (aerobic metabolism) decreases in skeletal muscle during early exercise [11-15]. These changes in metabolism are independent of muscle blood flow [11, 14, 15] and occur in CHF patients when compared with healthy subjects during exercise [11].

A decrease in oxidative type I fibers and an increase in glycolytic type IIb fibers [16-18], a decrease in myosin heavy-chain type I isoforms in proportion to peak oxygen consumption [19], a reduction in the levels of oxidative enzymes [17], an increase in adverse skeletal muscle mitochondrial change [18], an impaired peripheral vasodilatory capacity [93], a reduced peripheral blood flow [93-95], and a reduction in skeletal muscle capillary density [16, 18, 20] are among the other skeletal muscle changes in CHF patients that impaired oxygen extraction or substrate delivery/utilization by skeletal muscles resulting in reduced exercise tolerance, fatigue, and dyspnea.

Several studies have demonstrated that exercise training has many beneficial effects on impairments of the skeletal muscle (Table **4**) in CHF. Levinger *et al.* [96], reported a significant improvement in both lower limb and upper body strength ($P<0.05$), Peak VO2 ($P<0.05$), and quality of life ($p<0.05$) after 8 weeks of resistance exercise training in CHF patients. Other studies have also shown a significant increase in muscle strength [61, 66, 76, 97] and endurance ($P<0.005$) [97] after exercise training. Exercise training partially enhances the skeletal muscle metabolism in CHF patients [2, 66, 98, 99]. It reduces blood lactate level during sub-maximal exercise [2, 40] and increases oxidative capacity in relation to glycolytic (anaerobic) capacity in CHF patients [40].

Tyni-Lenne *et al.* [40], reported a marked statistically significant increase in citrate synthase activity ($p<0.0001$) as an indicator of oxidative capacity of muscle fibers. Their study also showed a significant increase in lactate dehydrogenase activity ($P<0.002$) as a result of exercise induced enlargement of type II fibers which contains 3 to 4 times higher levels of this enzyme than type I fibers, which is one of several glycolytic enzymes. As mentioned before, they reported an overall increase in oxidative capacity in relation to glycolytic capacity ($P<0.002$) after their exercise training program.

Table 4: Effects of Exercise Training on Skeletal Muscle and Blood Vessels in CHF Patients

	Exercise training effects
Skeletal muscle strength and endurance	Increase
Skeletal muscle metabolism	Increase
Oxidative capacity in relation to glycolytic capacity	Increase
Blood lactate level during sub-maximal exercise	Decrease
Mitochondrial volume density and surface area	Increase
Skeletal muscle fiber type distribution and size	Contrary results
Peripheral and myocardial blood flow	Increase
Endothelial function	Improve
Total peripheral resistance	Decrease
Capillary density(measured by capillary/fiber ratio)	Increase

Adamopoulos *et al.* [98] using phosphorus-31 nuclear magnetic resonance spectroscopy, revealed that exercise training decreased the phosphocreatine depletion and ADP during exercise, and improved the rate of phosphocreatine re-synthesis (independent of muscle mass). These changes indicate that exercise training improves skeletal muscle oxidative capacity in CHF patients. Magnusson *et al.* [99] directly studied the skeletal muscle changes after high intensity exercise training in CHF patients by needle biopsies. They reported an increase in muscle cross-sectional area, capillary per fiber ratio, and oxidative enzyme activity and unaltered glycolytic enzyme activity in trained muscles after exercise training.

Exercise training has been shown to increase mitochondrial volume density [45] and surface area [76, 100], without any change in the number of mitochondria. It also increases the surface density of mitochondrial cristae and also surface density of the mitochondrial inner border membrane. These changes lead to increased mitochondrial content (oxidative enzymes) and resultant improvement in oxidative capacity in skeletal muscles and are correlated with improvement in exercise intolerance in CHF patients. Again, these changes are independent relative to the degree of peripheral perfusion.

Some studies have shown contrary results for effects of exercise training on muscle fiber type, distribution, and size in CHF patients. Hambrecht *et al.* [100], reported a significant ($P<0.05$) increase in type I and a simultaneous significant decrease in type II fibers after 6 months of endurance exercise training. Belardinelli *et al.* [45], demonstrated a significant increase in both type I ($P<0.04$) and type II ($P<0.0001$) fibers cross-sectional area without any change in percent distribution of both fiber types after 8 weeks of low intensity exercise training. Inconsistent with these two mentioned reports, Larsen *et al.* [101], showed an overall significant decrease in muscle area ($P=0.003$) and an increase in interstitium after 12 weeks of exercise training. Their study also showed a trend toward increase in thickness of type IIB fibers ($P=0.068$) and a trend toward decrease in type I area ($P=0.062$). The differences between the results of these studies might be due to the differences in training level and duration in the studies.

Several studies demonstrated that exercise training enhances the peripheral and myocardial blood flow as well as endothelial function [47, 71, 97, 102-107]. Exercise training increases basal endothelial nitric oxide (NO) formation [105, 107] and improves peripheral blood flow through enhancement of endothelium mediated vasodilation of the peripheral vasculature [2, 105-107]. This exercise induced improvement in endothelial dysfunction has been reported to significantly increase exercise capacity ($r=0.64$, $P<0.005$) [105]. There is also a marked reduction in total peripheral resistance (TPR) during peak exercise after exercise training [47].

A study of an individual with total artificial heart (TAH) [173], confined to a constant cardiac output, despite changes in demand during exercise shows similar changes mentioned above. The patient experienced a 24% increase of peak oxygen consumption and an improvement in recovery kinetics during the training period of 29 months. Thus, more evident, that these changes are independent relative to the degree of peripheral perfusion.

In an experimental model of CHF in dogs with pacing-induced heart failure [107], Wang *et al.* reported an improvement in coronary artery dilatation that was mediated by enhanced endothelial function after exercise training. Santos *et al.* [102] showed an increase in myocardial blood flow (MBF) reserve, as an indicator of myocardial perfusion, after exercise training. Pietila *et al.* [104] reported an improvement in MBF after exercise training only in areas of low initial perfusion in CHF patients with concomitant coronary artery disease. They did not find a global increase in MBF. Exercise training has been associated with

increased capillary density as measured by capillary/fiber ratio [99, 101, 108]. Larsen *et al.* [101] also reported a correlation between increased capillary density and improvement in 6-min walk test as an indicator of exercise tolerance.

ET & AUTONOMIC SYSTEM & HORMONES

Through the body's effort to reverse the effects of decreased cardiac output and organ perfusion, several hormonal and neuro-humoral adaptations have arisen in CHF [109-111] that actually lead to worsening of the condition [112]. An increase in circulating levels of catecholamine as a result of sympathetic hyperactivity [109-111], a decrease in parasympathetic activity, a decrease in heart rate variability and baroreflex sensitivity [113-115], and an elevation in aldosterone, natriuretic peptides, angiotensin II (Ang II), and vasopressin levels [109, 112] are among several changes that occur in CHF patients. Several studies in animals and humans have demonstrated that exercise training can partially normalize the aforementioned changes in CHF. Studies on experimental models of HF have revealed that exercise training reduces sympathetic over-activity, reduces plasma levels of Ang II, and normalizes arterial baroreflex sensitivity [116-118], cardiopulmonary reflex sensitivity [119], and peripheral chemoreflex function [120].

Studies in CHF patients have shown the beneficial effects of exercise on these neuro-humoral derangements (Table **5**). Several studies [33, 47, 88, 121] reported a significant reduction in resting norepinephrine plasma levels after exercise training and another study by Gordon *et al.* [121], showed a significant ($P<0.05$) decrease in norepinephrine only during submaximal exercise.

Hembrecht *et al.* [47], reported a significant reduction of resting epinephrine plasma levels ($P=0.03$) and also a trend toward a decrease in plasma levels of norepinephrine at rest and during submaximal exercise after exercise training. Another study by Tyni-Lenne *et al.* [122], showed a significant reduction in plasma levels of norepinephrine both at rest ($P<0.003$) and during sub peak exercise ($P=0.03$) after comprehensive local muscle training in patients with stable, moderate CHF. Exercise training can also reduce the muscle's sympathetic nerve activity [46, 123].

Exercise training reverses the autonomic dysfunction and produces a significant shift from sympathetic over-activity to enhanced vagal activity

Table 5: Effects of Exercise Training on Autonomic System and Hormones in CHF Patients

	Exercise training effects
Sympathetic overactivity	Decrease
Plasma levels of Angiotensin II	Decrease
Baroreflex sensitivity	Increase
Vagal tone	Increase
Heart rate variability	Increase
Cardiopulmonary reflex sensitivity	Increase
Peripheral chemoreflex function	Decrease
Resting norepinephrine plasma levels	Decrease
Resting epinephrine plasma levels	Decrease
Muscle sympathetic nerve activity	Decrease
Resting levels of Angiotensin II	Decrease
Resting levels of vasopressin	Decrease
Resting levels of aldosterone	Decrease
Resting levels of atrial natriuretic peptide	Decrease

[33]. The enhancement of vagal tone after exercise training has been demonstrated by the improvement in baroreflex sensitivity [104] and also by an increase in heart rate variability [33, 124, 125]. Exercise training also has beneficial effects on reducing the indices of ventricular repolarization dispersion [126] in CHF patients. This reduction may lessen the risk of malignant ventricular arrhythmias and sudden death in this group of patients.

As mentioned above, exercise training can also modify the hormonal imbalances in patients with CHF. Braith *et al.* study [55], revealed a significant decrease ($P<0.001$) in resting levels of angiotensin II, vasopressin, aldosterone, and atrial natriuretic peptide after exercise training in this group of patients.

ET & ERGOREFLEX, THE MISSING LINK BETWEEN PERIPHERAL AND CENTRAL EFFECTS

Ergoreceptors, located on the chemo sensitive small myelinated or unmyelinated afferent nerve endings which reside in muscle interstitium, are partially involved in regulation of autonomic, hemodynamic, andventilatory responses to exercise. They are sensitive to muscle metabolic products, such as bradykinin, prostaglandin, and hydrogen ions and their excessive activation in CHF patients may contribute to abnormalities in aforementioned responses above and reduction in exercise capacity observed in this group of patients [127-135].

Piepoli *et al.* [136] showed that the decrease in sympathetic over activation and ventilatory drive after exercise training in CHF patients may be partially mediated through reduction in ergoreceptor activation as a result of enhancement of peripheral skeletal muscle metabolism with a decrease in acidification.

ET & INFLAMMATION

One of the important factors in CHF pathophysiology is increased inflammatory response. There is an increase in plasma levels of chemotactic cytokines, such as macrophage inflammatory protein 1α and macrophage chemo-attractant protein I [137], and also important pro-inflammatory cytokines, such as interleukin 6 (IL-6) and tumor necrosis factor (TNF) [138, 139] in CHF patients.

The activation of cytokines can have a negative effect on myocardial contractility through activation of nitric oxide synthase (iNOS), which inhibits the release of Ca^{2+} from sarcoplasmic reticulum and augments the expression of phospholamban. As a result, there is increase in oxidative stress, which promotes cardiac remodeling and apoptosis of myocytes [140-142]. Cytokine production can also result in endothelial dysfunction by promoting endothelial cell apoptosis [143], increasing reactive oxygen species production [144], and enhancing endothelial adhesion molecule expression, including vascular cell adhesion molecule I and intercellular adhesion molecule I [145]. Elevated cytokine levels in CHF patients also have a negative impact on the skeletal muscle metabolism and contractility. High cytokine levels reduce insulin-like growth factor I expression in skeletal muscles, promote oxidative stress and apoptosis of skeletal muscle myocytes. The induced expression of iNOS results in increased intracellular NO which impairs aerobic metabolism in skeletal muscle through inhibition of key enzymes of the respiratory chain [146-148]. Thus, sustained high levels of cytokines will eventually lead to muscle wasting and catabolism in CHF patients [149].

Several studies have shown that exercise training has an anti-inflammatory effect in patients who suffer from CHF. In experimental CHF models, exercise training increases anti-inflammatory cytokines such as IL-10 plasma levels [150] and IL-2 production [151], thus suppressing macrophage [152] and lymphocyte [151] activation.

To summarize, exercise training in CHF patients demonstrates a significant reduction in plasma levels of pro-inflammatory cytokines (TNFα, soluble TNF receptor I and II, IL-6, soluble IL-6 receptor [153, 154]), apoptosis mediators (soluble Fas (P=0.05) and soluble Fas Ligand (P<0.05) [154]), peripheral inflammatory markers of endothelial dysfunction (macrophage chemo attractant protein-1 (MCP-1) (P<0.001), granulocyte-macrophage colony-stimulating factor (GM-CSF) (P<0.001), soluble intercellular adhesion molecule-1(sICAM-1) (P<0.01), soluble vascular cell adhesion molecule-1 (sVCAM-1) (P<0.01) [155]), and also platelet-mediated inflammatory markers (P-Selectin and CD40 Ligand) [156]. In addition to decreasing pro-inflammatory cytokines, exercise training also reduces iNOS expression. This change leads to a reduction in inflammation within skeletal muscles, reverses muscle catabolism and wasting, increases muscle force generation, and enhances the activity of key enzymes withinrespiratory chain key to improved skeletal muscle aerobic metabolism [48, 157]. Thus, exercise training can be considered an anti-inflammatory therapeutic regimen for patients with CHF.

ET & BNP

Brain natriuretic peptide (BNP) level, is elevated in CHF patients. BNP, a cardiac neurohormone, is initially secreted as pre-pro-BNP in response to stretching of ventricular myocytes and is cleaved enzymatically into BNP and N-terminal-proBNP. BNP blood levels have been used as a measure to identify CHF patients [158, 159] and BNP assays have been shown to have both diagnostic and prognostic values in CHF [159, 160].

A recent systemic review of nine randomized controlled studies which measured the effects of exercise training on BNP or NT-pro-BNP levels by Smart *et al.* [161], has shown that exercise training with a weekly exercise energy expenditure of more than 400 Kcal, significantly reduces the BNP and NT-pro-BNP in patients with CHF.

ET & IRON DEFICIENCY

Iron is an indispensable element of hemoglobin, myoglobin, and cytochromes, and, beyond erythropoiesis, is involved in oxidative metabolism and cellular energetics. Hence, iron deficiency (ID) is anticipated to limit exercise capacity [176]. Jankowska *et al.* studied 443 patients. ID was defined as: serum ferritin <100 ug/L or serum ferritin 100-300 ug/L with serum transferrin saturation <20%. Exercise capacity

was expressed as peak oxygen consumption (VO2) and ventilator response to exercise (VE-VCO2 slope). ID was present in 35 ± 4% (± 95% confidence interval) of patients with systolic CHF. Those with ID had a reduced peak VO2 and increased VE-VCO2 slope as compared to subjects without ID (peak VO2: 13.3 ± 4.0 versus 15.3 ± 4.5 mL*min*kg, VE-VCO2 slope:50.9 ± 15.8 versus 43.1 ± 11.1, respectively, both $P < .001$, $P < .05$). Thus, ID independently predicts exercise intolerance in patients with systolic CHF.

ET & QUALITY OF LIFE (QOL) & SURVIVAL

CHF is a common health issue in United States with a significant morbidity and mortality especially in advanced age [162] that progressively leads to worsening disability and decreased QOL in patients suffering from it [130, 163, 164].

Different trials and meta-analyses have shown different results regarding the beneficial effects of exercise training on decreasing mortality and hospitalization and improving QOL in CHF patients.

Belardinelli *et al.* studied [35] the benefits of moderate intensity exercise training in 94 of 99 enrolled patients over a 14 month period. They reported asignificant decrease in mortality rate (P=0.01) and hospital readmissions for heart failure (P=0.02). The exercise group also had a significant improvement in QOL (P<0.001) as assessed with the Minnesota Living with HeartFailure Questionnaire. A meta-analysis by Piepoli *et al.* of nine randomized controlled trials including the above mentioned study with the total number of 801 patients [165], showed a significant reduction in mortality and hospitalization after exercise training.

HF-ACTION [59] is the largest randomized controlled trial evaluating the effect of exercise training in patients with heart failure. This trial has studied 2331 patients, and has reported contrasting results in terms of exercise effects on mortality and hospitalization rate. The HF-ACTION study did not show a significant decrease in all-cause mortality and hospitalization after exercise training. There was an association between exercise training and an average significant decreases in cardiovascular mortality or heart failure hospitalization (P=0.03) and all-cause mortality or hospitalization (P=0.03), after adjusting for highly prognostic predictors of the primary end point (left ventricular ejection fraction, duration of the cardiopulmonary exercise test, history of atrial fibrillation or flutter, and Beck Depression Inventory II score). The interpretation of the HF-ACTION is complex and has to take into consideration the following: 1) the control group was not without any physical activity; in fact, in keeping with the American College of Cardiology/American Heart Association guidelines, patients randomized to this group were recommended to perform 30 min (or as long as can be tolerated) of moderate intensity activity on most days of the week; 2) compliance with exercise training in the trained group was relatively low: close to 60 min/week on average of exercise time instead of the 120 min/week expected; 3) patients in the training group had a relative low gain in peak VO2 (0.6 ml/kg/min = 4% vs. 17% on average observed in other controlled studies [57]. This, together with other results suggests that change in exercise capacity is a strong prognostic factor in CHF patients [54]. The most recent Cochrane systemic review and meta-analysis (updated from the previous review [166] in 2004) of nineteen randomized controlled trials of exercise training for systolic heart failure with a minimum follow up of six month (including HF-ACTION study) with a total number of 3647 patients by Davies *et al.* [167], has shown that exercise training has no significant effect on all-cause mortality or overall hospital admissions, but improves health related quality of life (HRQOL: assessed by a validated outcome measure) and reduces hospitalizations related to heart failure in this group of patients.

A review from Lloyd-Williams *et al*. [168], showed an improvement in QOL among 11 of 16 studies after exercise training in chronic heart failure patients. An average of a 9.7 point improvement in Minnesota Living with Heart Failure Questionnaire was reported in a more recent meta-analysis of 35 randomized controlled trials of exercise training for heart failure patients by Van Tol *et al*. [86] Flynn *et al.* (HF-ACTION) [68], also reported a significant (P<0.001) improvement in self-reported health status of heart failure patients after exercise training using KCCQ (Kansas City Cardiomyopathy Questionnaire) as an assessment tool.

INDICATION FOR ET

Most of the studies on exercise training have been performed in CHF patients with LVEF less than 40% in NYHA functional class II or III. Guidelines recommend cardiac rehabilitation in such patients [54, 169, 170]. No data are available concerning CHF patients with preserved left ventricular function and in those with asymptomatic CHF. Similarly, there is a lack of

information on the effect of exercise training on CHF patients with NYHA functional class IV; thus this patient population is currently excluded from cardiac rehabilitation programs. Exercise training benefits patients with ischemic and non-ischemic etiology, although improvement in peak VO2 has been reported to be greater in patients with non-ischemic cardiomyopathy [28].

CONCLUSIONS

The current evidence surrounding several studies clearly indicate that exercise training is a safe, valuable and effective treatment in the management of CHF patients. Exercise training also has beneficial effects on the cardiovascular and autonomic system, the skeletal muscles, and the ventilation in these patients. Exercise training reverses the hormonal and inflammatory abnormalities. All together, these changes improve exercise tolerance and quality of life in CHF patients. It still remains questionable whether or not exercise training reduces mortality or hospitalization in patient with CHF [171].

DISCLOSURES

None.

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