

Exercise Training in Heart Failure, Clinical Evidences and Areas of Uncertainty

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in the prescription of exercise training in patients with chronic heart failure.

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ABSTRACT

Exercise training, as a part of a comprehensive rehabilitation program, is currently recommended in combination with pharmacological therapy in patients with chronic heart failure. Benefits of exercise training that have been evidenced by scientific literature include improvements in various aspects of physiological function, aerobic exercise capacity and quality of life. Despite exercise training has been included in European and American guidelines as class IA recommendation, at least three important aspects need to be clarified. First of all, the effectiveness of exercise training in improving long term prognosis of patients with chronic heart failure still remains a debatable point. Secondly, the majority of studies have investigated the effects of a particular modality of exercise: continuous aerobic training performed at mild to moderate intensity. On the contrary, the effects of other exercise modalities such as intermittent training, resistance training or hydrotherapy on chronic heart failure haven't been fully understood yet. Finally, patients included in clinical trials evaluating the effects of exercise training are, almost exclusively, those with reduced ejection fraction. Consequently very few data are, until now, available with regard to subjects with heart failure with preserved ejection fraction. This article summarizes the evidences and mechanisms by which exercise training can improve symptoms of heart failure. Moreover, it underlines current limits of knowledge

INTRODUCTION

Chronic heart failure (CHF) is a disease with an increasing prevalence, as a result of the ageing population; it determines a relevant social burden worldwide^[1].

CHF is characterized by a reduced exercise tolerance with patients often experiencing early fatigue and dyspnoea. Such symptoms impact upon their ability to perform activities of daily living and contribute to a poor quality of life and to a reduced patients' wellbeing. Symptoms of CHF have a complex origin, being related to both central and peripheral mechanisms. An impaired left ventricular (LV) function with reduced stroke volume and cardiac output, a prolonged and abnormal neurohumoral activation, endothelial dysfunction, a pro-inflammatory state and a metabolic imbalance favoring catabolism with impaired skeletal muscle bulk and function, are all involved in the onset of clinical manifestations of CHF as well as in the disease progression^[2].

Exercise training (ET) has been established as an effective adjuvant therapy in CHF by leading to an improvement of exercise tolerance and quality of life^[3,4]. ET exerts these beneficial effects by acting at different levels. While some studies have attributed this action to exercise-induced favorable changes in LV function and cardiac output^[5,6], others have identified peripheral adaptations in the

arterial and skeletal muscle function as the primary contributor to improvement in fitness after ET^[7,8].

Up until the late 1980s, ET was considered unsafe for patients with CHF because of worries about the possibility of further worsening contractile function and poor clinical outcomes. On the contrary, researches over last 25 years expanded our understanding and knowledge about the role of ET in CHF and ultimately demonstrated that exercise for these patients is not only safe but also provides substantial physiological and psychological benefits. As a result, European guidelines have incorporated a class IA recommendation for regular aerobic exercise in patients with CHF to improve functional capacity and symptoms^[9]. However, although the general concept that ET is a safe and effective treatment for CHF has been well established by now, many doubts still remain regarding the doses, modalities, long-term feasibility and lack of effectiveness of training programs.

Lastly, half of CHF patients have preserved ejection fraction (HFpEF) and there are still few clinical evidences about the effects of ET on this broad group of patients.

This review summarizes the evidence and mechanisms by which ET improves symptoms of CHF and underlines current limits of knowledge in the prescription of ET in CHF patients.

MECHANISMS OF ACTION OF EXERCISE TRAINING

Neurohormonal modulation

CHF is characterized by extreme vasoconstriction and redistribution of blood volume with a chronically diminished blood flow to the exercising muscles. These alterations are due to an abnormal activations of neurohumoral systems modulating vascular tone, including the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. Available data support the hypothesis that ET counteracts the abnormal activation of the neurohormonal systems, reducing vasoconstriction and increasing peripheral blood flow. ET reduces norepinephrine levels at rest and during exercise^[5], decreases central sympathetic nerve outflow measured directly by microneurography, enhances vagal control, and improves heart rate variability with the return to a more balanced sympathetic-vagal tone^[10]. ET reduces plasma Angiotensin II levels^[11] and modulate RAS activation at muscle level by reducing angiotensin II receptors T1 and by increasing Angiotensin-(1-7)/Angiotensin II ratio^[12]. ET reduces the natriuretic peptide overexpression with a significant reduction in brain natriuretic peptide (BNP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels^[13,14]. Smart *et al*^[15] performed a meta-analysis including ten randomized controlled studies and showed positive effects of ET on BNP (-28.3) and NT-proBNP (-37.4). Changes in BNP ($r = -0.31, p < 0.0001$) and NT-pro-BNP ($r = -0.22, p < 0.0001$) were inversely correlated with peak VO₂ change.

Endothelial dysfunction

Endothelial dysfunction has been documented in peripheral and coronary arteries in patients with CHF^[16] and consists of an impaired flow-dependent, endothelium-mediated vasodilation related to a reduced endothelial nitric oxide (NO) availability^[17]. Endothelial dysfunction has a pathophysiological role in CHF because it contributes to the abnormal vasoconstriction observed in these patients and it is related to lower exercise tolerance. Moreover, endothelial dysfunction results as an independent predictor of cardiac death and hospitalization^[18]. Katz *et al*^[19] and Parnel *et al*^[20] showed

that ET improved endothelial function and arterial compliance in CHF subjects, and the former effect was correlated with improvement in VO₂peak due to ET^[21,22]. The beneficial effects on endothelium were lost after ET suspension. In the study of Sarto *et al*^[23] patients with CHF showed enhanced endothelial progenitor cell (EPC) levels and plasma levels of vascular endothelial growth factor and stromal cell-derived factor after ET. Conversely, they returned to baseline levels after 8 weeks of training discontinuation.

Inflammation

Increased inflammatory response has been recognized as an important factor in the pathophysiology of CHF. Levels of major proinflammatory cytokines, such as Tumor Necrosis Factor (TNF) and Interleukin-6 (IL-6) are increased in CHF^[24,25]. Cytokine activation exerts several negative effects by reducing myocardial contractility, inducing activation of inducible Nitric Oxide Synthase (iNOS), increasing oxidative stress, inhibiting sarcoplasmic reticulum Ca²⁺ release and phospholamban expression, and promoting myocyte apoptosis and cardiac remodelling^[26,27]. The pro-inflammatory state also contributes to the onset of endothelial dysfunction^[28,29] and skeletal muscle catabolism and wasting^[30]. In patients with CHF, ET showed potential anti-inflammatory activity, by reducing plasma levels of inflammatory cytokines such as TNF, soluble TNF, IL-6, IL-6 receptor, IL-1 β ^[31] and platelet-related inflammatory mediators^[32]. An ET-mediated increase of plasma levels of the anti-inflammatory cytokine IL-10^[33] has also been reported. The mechanisms underlying the anti-inflammatory effect of ET are still largely unknown. Reduction of sympathetic outflow together with cholinergic activation induced by ET have been indicated as possible mediators of its anti-inflammatory activity^[34].

Glucose metabolism

Disorders of glucose metabolism, in particular diabetes, frequently occur in patients with CHF. Approximately 15% to 35% of CHF patients that have been enrolled in clinical trials were diabetic. Similarly, data from several registries showed an overall prevalence of diabetes in CHF of approximately 20-25%^[35]. The presence of diabetes in CHF has important prognostic implications: diabetic patients have lower exercise tolerance, an attenuated improvement in peak VO₂ after ET and higher morbidity and mortality compared to non diabetic patients^[36-38]. Consistent data suggest that the accumulation of advanced glycation end-products (AGEs) play a role in the onset of cardiac and vascular damage in diabetic patients. High AGEs levels have been associated with LV diastolic dysfunction and with reduced exercise tolerance in diabetic CHF patients^[39]. AGEs breakers seem to be able to reverse the structural changes that are related to diastolic dysfunction^[40]. Pentosidine, a marker of AGEs, and soluble receptors for AGE (sRAGE) resulted as independent prognostic factors in CHF^[41].

ET improves glucose homeostasis and insulin sensitivity in CHF. ET reduced fasting glucose, fasting insulin levels and insulin release during oral glucose tolerance test compared to controls^[42-44]. In the study of Kemppainen *et al*^[45] fifteen patients with dilated cardiomyopathy performed ET for 5 months at an intensity of 70% of VO₂ peak. Their exercise capacity improved with a concomitant enhancement in resting and exercising skeletal muscle glucose uptake. Interestingly, the improvement of insulin sensitivity was not related to changes in muscle perfusion suggesting an enhanced cellular glucose extraction.

Preliminary studies indicate that ET reduces levels of AGEs in diabetes. 12-weeks of aerobic exercise increased sRAGE levels

along with improvement of various cardiometabolic risk factors in women with diabetes^[46]. ET attenuated cardiac fibrosis and AGEs accumulation in rats^[47]. Though the anti-AGEs effect seems a promising mechanism of action for ET, data on CHF are still lacking; the exact proportion of cardiovascular benefits related to the ET-induced reduction of AGEs in diabetic CHF patients needs to be established yet.

Skeletal muscle

CHF subjects present intrinsic alterations of skeletal muscles that are similar to those observed in deconditioning/detraining and chronic obstructive pulmonary disease. Muscular alteration are in part responsible for the onset of exercise intolerance in CHF. Studies on skeletal muscle of CHF patients reported reduced oxidative capacity as compared to controls^[48,49], increased atrophy^[50], increased apoptosis^[51,52] and a fiber-type switch toward a less fatigue-resistant phenotype. Moreover a pro-inflammatory state of skeletal muscles, with increased local expression of IL-1b, TNF-alpha and IL-6 has also been described in CHF rat models^[53] as well as in CHF patients^[54,55].

As a consequence of the structural and metabolic changes occurring in the contracting muscle of CHF patients, an exaggerated exercise pressor reflex is triggered in skeletal muscles and this significantly contributes to the elevate sympathetic tone, to the abnormal regulation of the cardiovascular system and to the ventilatory response to exercise in CHF^[56].

A six months ET program, performed at 70% of maximal heart rate, led to a significant increase in muscle aerobic capacity, with a significant increase in myofibril cross-sectional area, mitochondrial density and capillary density^[57]. Oxidative capacity of the muscle improved as reflected either by increased activity of key aerobic enzymes^[58] or by an increase of intracellular pH and phosphocreatin levels both at rest and during work^[59]. ET turned out to reduce oxidative stress and the levels of inflammatory cytokines in skeletal muscle^[60]. Intrinsic skeletal muscle alterations appear to be totally reversible by ET: two studies compared training effects on skeletal muscle properties of CHF patients to that of the healthy, age-matched population: they showed that pre-training alterations in skeletal muscle normalized compared to controls after few weeks of training^[61,62]. These modifications of skeletal muscles appear even with low intensity endurance exercise training (i.e., 40% of peak VO₂) and contribute to a significant improvement in both peak VO₂ and ventilatory threshold^[63].

Wang *et al*^[64] observed that 8 to 10 weeks of ET significantly improved the exaggerate responses induced by skeletal muscle static contraction or passive stretch in CHF rats, by enhancing the mechanical component and partially improving the metaboreflex control of blood pressure.

Cardiac effects

The effects of ET on central haemodynamic function are less well established. Early studies demonstrated scarce or no effect on haemodynamic parameters. In the study of Sullivan *et al*^[65] 12 patients with CHF underwent direct hemodynamic monitoring before and after training. Resting and exercise right atrial pressure, pulmonary capillary wedge pressure and pulmonary artery pressures resulted to be unchanged after training. Stroke volume had small, not significant, increase after training.

Cardiac output response to aerobic training in CHF patients has been evaluated by relatively few studies and most of them have shown a significant increase of cardiac output at peak effort after

a period of training compared with pre-training values. The meta-analysis of Van Tol *et al*^[66] quantified the effect of ET on cardiac output, demonstrating a significant mean increment of 2.5 L/min (21% compared to pre-training) in a total of 104 CHF patients after training.

Clinical trials showed heterogeneous results on cardiac dimension and function measured by echocardiography. Resting left ventricular end-diastolic volume (LVEDV) has been shown not to change^[65,67] or even to be reduced^[68,69] after a period of aerobic training in CHF patients. Similarly to LVEDV, left ventricular ejection fraction (LVEF) was unchanged^[70,71] or increased^[68] after training compared to pre-training values. Overall, research studies indicated an anti-remodeling effect of ET. The meta-analysis of Haykowsky *et al*^[72] including 14 trials (812 patients) demonstrated that moderate intensity ET led to a significant improvement of LVEF (+2.59%), LVED (-11.5 mL), and LV end-systolic volume (LVESV) (-12.87 mL), compared with usual care. However, only seven out of 14 trials reported data on LVEDV and LVESV, and the use of beta-blockers in the studies included in the analysis was low.

The anti-remodeling effects of ET were confirmed by Chen *et al*^[73] who evaluated 15 studies for a total of 813 patients, observing that only long-term aerobic exercise (>6 months) had a marked positive effect on LVEDV [standardized mean difference (SMD) = -0.38; 95% CI -0.57 to -0.19] and LVESV (SMD -0,48 95% CI -0,67 to -0,29), while there was no evidence of benefit with ET programs of short-term duration (<6 months).

LV diastolic dysfunction is often present in CHF and is an important determinant of symptoms. In patients with diastolic dysfunction, ventricular distensibility during exercise is impaired, resulting in a rapid rise in LV diastolic pressure and pulmonary capillary wedge pressure and the subsequent experience of dyspnea. ET improved LV diastolic filling patterns in CHF. In the study of Belardinelli *et al*^[71] a two-months ET program determined a significant increase of early filling velocity (E), and E/A ratio.

EXERCISE TRAINING IMPROVES AEROBIC CAPACITY IN CHF

A significant limitation of the maximal aerobic capacity typically occurs in subjects with CHF. When compared with age matched normal controls, these patients present a reduced oxygen consumption at maximal effort (VO₂ peak), an early onset of the anaerobic threshold and an excessive increase in minute ventilation with exercise, out of proportion to the increase in carbon dioxide production (VE/VCO₂ slope). Because these parameters are strong predictors of survival in CHF patients^[74,75], they represent therapeutic targets of primary importance.

Aerobic continuous ET, performed at mild-moderate intensities, improves the aerobic capacity of CHF patients. The majority of studies demonstrated an improvement in VO₂peak ranging between 15% and 25%. Rees *et al*^[76] performed a systematic review of randomized controlled trials (RCTs) evaluating the effects of ET in CHF. The review included a total of 1,226 patients and demonstrated a mean increase of 2.16 ml/kg/min in VO₂ peak. An increase in exercise time and anaerobic threshold has also been observed^[77]. The ventilation to carbon dioxide production slope (VE/CO₂), has also been shown to consistently improve with ET^[78].

The improvement of exercise tolerance obtained by ET has positive repercussions on patients' life. As patients become more tolerant to exertion, they experience less fatigue and dyspnoea and become more comfortable performing tasks of daily living. Such a

response is associated with increased independence, better mood, and improvement of their quality of life^[79,80].

IMPACT OF EXERCISE TRAINING ON SURVIVAL AND REHOSPITALIZATION

Until 2009, survival and hospitalization were reported by several small trials that were largely underpowered for analyzing such prognostical endpoints. Nine of these trials were included in the meta-analysis of Piepoli *et al*^[81] that evaluated a total of 801 patients; 395 out of 801 received ET and 406 were controls. During a mean follow up of 705 days 88 deaths have been observed in the exercise arm and 105 in the control arm. The median time to admission to hospital was 426 days in the exercise arm and 371 days in the control arm, with a significant benefit in the exercise arm ($p = 0.011$). Authors evidenced a 35% ($p < 0.05$) lower risk for mortality and a 28% ($p < 0.05$) lower risk for the composite endpoint of mortality or hospitalization in favor of ET, with a number needed to treat of 17 to prevent one death in two years.

Another meta-analysis published the same year^[82] evaluated 30 parallel groups RCTs, including a total of 1,197 patients. Their training duration ranged from 15 minutes 3 times/week for 8 weeks to 100 minutes 7 times/week for 8 weeks. The follow up ranged from 4 weeks to 192 weeks. Groups did not differ for adverse events or all cause mortality (Table 1). For all included trials, no exercise related death occurred in any patient during the training period.

Despite their promising results, these meta-analyses present important limitations: firstly, none of the studies included had sufficient power to address hard endpoints; in the second instance, most of the studies were small single-centre trials.

The HF-ACTION^[83] was the largest RCT including 2,331 outpatients with CHF with a mean age of 59 years. Patients were randomized to either 36 sessions of supervised, moderate intensity training (60% to 70% heart rate reserve) followed by home-based

training or usual care. All subjects were followed for a median of 30 months. A modest but significant improvement in measured peak VO2 was evidenced in the exercise group compared with the control group (0.6 mL/kg/min vs 0.2 mL/kg/min, respectively) at 3 months. In this study non-significant reductions for mortality occurred in ET group (189 patients,16%) vs control group (198 patients, 17%); (HR, 0.96; 95% CI = 0.79-1.17; $p = 0.70$). Similarly, cardiovascular mortality and cardiovascular hospitalization did not differ between training and control group. Several explanations for the negative results of this trial have been put forward; these include usual care crossover but also the high percentage of patients in both groups using evidence-based medical treatment. However, the major flaw has been the very low level of adherence to the prescribed exercise regimens, whereby less than 40% of subjects exercised at the target number of 1.5 hours/week or above it, for the first three months, resulting in a smaller improvement in aerobic capacity compared to other trials.

Swank *et al*^[84] observed that in the HF-ACTION population the subgroup of subjects who had a greater increase of VO2 peak (and a greater compliance) presented also a better prognosis. Authors observed that every 6% increase in VO2 peak was associated with a 5% lower risk of the primary endpoint (all-cause mortality or all-cause hospitalization) (HR = 0.95; CI=0.93-0.98; $p < 0.001$) and a 7% lower all-cause mortality (HR = 0.93; CI 0.90-0.97; $p < 0.001$).

AREAS OF UNCERTAINTY

Prescription of training program

Up until now, there are no clearly delineated practical guidelines for exercise prescription in the setting of CHF, resulting in a variety of centre-specific approaches for these patients. Study designs have varied significantly with respect to the type of exercise performed. Some have included individual activities such as cycle ergometer or treadmill alone, while others have investigated combination therapies

Table 1 Overview of meta-analyses evaluating effects of ET on cardiac performance, exercise tolerance and prognosis of patients with CHF.

Study	Trials included	HF type	Patients included	Endpoints	Results	Conclusions
Van Tol <i>et al</i> (2006) ^[66]	35	HFrEF	1,486	LVEF LVEDV (ml) LVESV (ml) CO CO (peak exercise)	SES= 0.16; 95% CI 0.12 to 0.45 SES= 0.21; 95% CI 0.39 to 0.04 SES= 0.26; 95% CI 0.58 to 0.07 SES= 0.27; 95% CI 0.08 to 0.61 SES= 0.58; 95% CI 0.19 to 0.97	Small positive effects on cardiac performance during exercise
Haykowsky <i>et al</i> (2007) ^[72]	14	HFrEF	812	LVEF (%) LVEDV (ml) LVESV (ml)	WMD=2.59%; 95% CI 1.44 to 3.74 WMD= -11.5; 95% CI -19.9 to -3.02 WMD= -12.9; 95% CI -17.8 to -7.9)	Aerobic ET reversed LV remodeling
Chen <i>et al</i> (2012) ^[73]	15	HFrEF	813	LVEF (%) LVEDV (ml) LVESV (ml)	SMD=0.44; 95% CI 0.28 to 0.61 SMD=-0.33; 95% CI -0.49 to -0.16 SMD=-0.40; 95% CI -0.57 to -0.23	Long term (> 6 months) aerobic ET reversed LV remodeling
Rees <i>et al</i> (2004) ^[76]	29	HFrEF	1,126	VO2 peak Time exercise Work capacity 6MWT distance	WMD= 2.16; 95%CI 2.82 to 1.49 WMD= 2.38; 95%CI 2.8 to 1.9 WMD= 15.1; 95% CI 17.7 to 12.6 WMD=40.9; 95% CI 64.7 to 17.1	ET Improved exercise tolerance
Piepoli <i>et al</i> (2004) ^[81]	9	HFrEF	801	Mortality Combined endpoint	HR= 0.65; 95% CI 0.46 to 0.92 HR= 0.72; 95% CI 0.56 to 0.93	ET reduced mortality
Smart <i>et al</i> (2004) ^[82]	30	HFrEF	1,197	Adverse events All cause mortality Combined endpoint	OR= 0.83; 95% CI 0.50 to 1.39 OR=0.71; 95% CI 0.37 to 1.02 OR=98; 95% CI 0.61 to 1.32	ET was safe compared to controls
Pandey <i>et al</i> (2015) ^[115]	6	HFpEF	276	VO2 peak E/A MLWHF	WMD= 2.72; 95% CI 1.79 to 3.65 WMD= 0.08; 95% CI -0.01 to 0.16 WMD= -3.97; 95% CI -7.21 to -0.72	ET Increased exercise tolerance. ET determined no changes on systolic or diastolic function

HFrEF= heart failure with reduced ejection fraction; HFpEF= heart failure with preserved ejection fraction; SES= summary effect size; SMD= standardized mean difference; WMD= weighted mean difference; 6MWT= six minute walk test; HR= hazard ratio; OR= Odds ratio; LVEF= left ventricular ejection fraction; LVEDV= left ventricular end diastolic volume; LVESV= left ventricular end systolic volume; CO= cardiac output; MLWHF= minnesota living with heart failure.

such as cycle ergometer plus additional activities such as rowing machines, step aerobics. Moreover, training studies have an extensive variability in duration and frequency of exercise applied (ranging from 10 min to 60 min sessions, performed between 3 to 7 times per week)^[85]. Therefore, despite the classical training programs proposed for CHF patients consist of aerobic endurance training sessions, the best weekly “dose” of training to be administered in terms of frequency of sessions and intensity of training has not been fully established yet. Notably, data from the majority of studies, including the HF-ACTION and trials included in the ExTraMATCH have been obtained from patients trained with continuous, mild/moderate training. There are however reports indicating that additional benefits can be obtained by using different training intensities and/or training modalities.

Interval training

Interval training (IT) consists of periods of high intensity exercise interspersed with recovery periods in which subjects have to re-engage in high-intensity exercise multiple times during the same session. The rationale is to spend more time in high-intensity zones compared to a continuous exercise in order to produce a stronger stimulus for cardiovascular and muscular adaptations^[86,87]. Wisloff *et al.*^[88] observed a significant increase of VO₂ peak compared to continuous training (46 % vs 14 %, $p < 0.001$) and a concomitant improvement of several cardiac parameters including LV ejection fraction (35 % increase) and BNP levels (40% decrease) with IT compared to continuous training in a small group of elderly patients with CHF. Similar results have been obtained by other authors^[89-91] suggesting the overall impression that IT induces many short- and long-term central and peripheral adaptations which are superior to those achievable by continuous training. However trial results are not univocal. By using a protocol of 30/30 seconds work/recovery intervals at high intensity (100 % of VO₂max) and passive recovery, Dimopoulos *et al.*^[92] found only a modest 8 % increase in VO₂ peak in the interval group compared to 6% in the continuous group without significant between groups differences.

Our group tested the hypothesis that the different results observed with interval versus continuous training could be related to different training loads rather than to different exercise modalities. We used the individualized training impulses method described by Manzi *et al.*^[93] to provide patients with equivalent doses of exercise in terms of volume/intensity either with interval and continuous training. We observed that, at equal training loads, changes of peak VO₂, anaerobic threshold, VE/VCO₂ slope and heart rate were not significantly different between interval and continuous training^[94].

Resistance training

Resistance training (RT) is a training modality that is particularly useful for maintaining and/or increasing muscle mass and strength in CHF patients because of its demonstrated effectiveness on preventing the decline in skeletal muscle mass and function associated with aging^[95]. Despite since the late 1990s an increasing number of clinical researches have been conducted on resistance exercise in CHF, the prescription of RT has been limited in relation to concerns for worsening the impairment of LV function and adverse LV remodeling caused by increased afterload during the lifting phase. However, low-intensity RT (performed at 40-60% of maximum voluntary contraction) with 15-20 repetitions, is well tolerated in CHF, leading to only modest elevations in blood pressure, similar to those seen during moderate endurance training^[96].

Studies on RT demonstrated that this training modality is associated

with several clinical benefits on CHF. It has been evidenced that RT exerts anti-inflammatory effects^[97], improves insulin resistance^[98] and counteracts loss of skeletal muscle mass and strength^[99]. In the study of Savage *et al.*^[100] 18-weeks of RT improved the performance of activities of daily living in CHF patients. Beckers *et al.*^[101] compared a combined endurance-resistance training with endurance training alone and found that, after six months, the combined training had a more pronounced effect on submaximal exercise capacity, muscle strength, and quality of life compared to endurance training alone. Conversely there were no differences with regard to the improvement of VO₂ peak, LVEF, LV dimensions between the two groups.

Hydrotherapy

Hydrotherapy represents a possible alternative for those patients for whom land-based training programs are not suitable. This category includes frail elderly and those with comorbid conditions including chronic pain and orthopedic or balance disturbances. Hydrotherapy consists of aquatic exercise during which patients are immersed in warm water. Until now few small trials, using different protocols have been conducted regarding the effects of hydrotherapy on CHF; overall they demonstrated improvement of VO₂ peak, 6-Minute Walk Test (6MWT) distance, muscle strength and quality of life while they did not show significant effects on cardiac dimension, ejection fraction and BNP levels. A recent meta-analysis of eight studies including a total of 156 patients, showed that benefits induced by hydrotherapy on exercise tolerance were not superior compared to those observed in controls undertaking usual activity^[102]. However, greater effects can be obtained by the combination of hydrotherapy and traditional exercise on land.

Our group, after 24 weeks of a combined training approach (aquatic + land training), observed a greater increase of VO₂ peak and 6MWT distance in the combined training compared to controls performing only ET on land. Moreover, only the combined training group presented a significant reduction of systemic vascular resistance and diastolic blood pressure^[103].

Anyway, it still remains to be established whether hydrotherapy represents a mere alternative for subjects who are unable to perform traditional ET on land or it could be effective in giving additional benefits to CHF patients.

Hydrotherapy seems to be a safe training modality for CHF patients: no adverse events were reported in any of the studies included in the meta-analysis of Adsett *et al.*^[102]. However, no definitive conclusions can be drawn given the small number of subject treated with hydrotherapy and the selective inclusion criteria used in trials.

Lack of improvement after exercise training

Patients with CHF have been considered as a homogeneous group in relation to their response to ET programs. However, some CHF patients show limited improvement in exercise capacity after performing ET. This could be easily understood by analyzing the results of several trials that showed minimal or no increase in peak exercise VO₂ after ET in some CHF patients. Belardinelli *et al.*^[71] enrolled 36 patients in a cardiac rehabilitation program and noted a 12% overall significant increase in peak exercise VO₂. However, they observed that most patients showed no improvement in peak exercise VO₂. Similarly, Coats *et al.*^[104] noted a 19% to 20% increase in peak exercise VO₂ in a group of 17 CHF subjects performing an home-based training program, but this was primarily caused by improvements in approximately one third of the patients.

The degree of response to ET has important prognostical

implications because lack of response is associated to poorer clinical outcomes. According to a prospective survey conducted on 155 subjects with CHF, patients who showed an improvement of VO₂ peak <2 mL/kg/min after ET had a lower event-free survival compared to good responders. In this study non-responders to ET were more often admitted to hospital for atrial fibrillation, had a slightly lower LVEF and showed a significantly lower chronotropic reserve and heart rate recovery compared with responders^[105]. Mechanisms underlying the so called resistance to ET still remain largely unknown. Schmid *et al*^[106] found that non-responders had chronotropic incompetence. Our group observed that non-responders were patients with higher comorbidities and lower compliance^[107]. Wilson *et al*^[108] studied the hemodynamic responses to treadmill exercise by invasive procedures in a group of patients with CHF enrolled in a standard cardiac rehabilitation program. They had observed that patients with CHF and exercise intolerance exhibited severe hemodynamic dysfunction during exercise, whereas others had normal cardiac output responses to exercise. Despite some possible causes have been recently elucidated, predicting the response to an exercise program in a given patient still remains a difficult task.

Heart failure with preserved ejection fraction

Exercise intolerance is the primary symptom of HFpEF and an important determinant of quality of life^[109]. As HFpEF shares with HFrEF several pathological mechanisms, there is a rationale for considering ET as a therapeutic strategy in these patients. Some recent studies have evaluated ET in patients with HFpEF^[110-113]; they have demonstrated a variable degree of improvement in exercise tolerance and diastolic function in response to training. A first meta-analysis by Taylor *et al*^[114] that included randomized and nonrandomized clinical trials, observed that changes in exercise capacity were higher in ET groups compared to controls (between groups weighted mean difference (WMD): = 3.0 mL/kg/min, 95% CI: 2.4 to 2.6). The E/E' ratio was unchanged in ET and controls. No safety concerns were raised because no serious adverse events occurred during or immediately following ET.

In a more recent meta-analysis, Pandey *et al*^[115] included 6 clinical trials, with a total of 276 patients. They showed that ET improved maximal exercise capacity (WMD = 2.72; 95% CI = 1.79 to 3.65) and quality of life (WMD = -3.97; 95% CI = -7.21 to -0.72) when compared with control group. Conversely, ET was not associated with any significant change in resting diastolic or systolic function. The study reported only few minor adverse events (transient hypoglycemia, muscle discomfort or dyspnoea). These results suggest two considerations: firstly, ET improves exercise tolerance in patients with HFpEF through mechanisms that are independent of LV function; in second instance, it can be safely performed by these patients. However studies included in this meta-analysis had a short duration with follow up ranging from 12 to 24 weeks, and the total number of HFpEF patients enrolled was too small. Therefore, available data on effectiveness and safety of ET can be considered preliminary results.

Additional studies with longer follow-up duration and addressing clinical endpoints, such as HF hospitalizations and mortality, should be performed in order to better clarify mechanisms of action of ET and whether it can be used as an effective strategy for the management of these patients.

CONCLUSION

Most of evidences support the benefits and safety of continuous

mild to moderate intensity ET for HFrEF patients who are receiving optimal medical therapy. ET leads to an improvement of exercise tolerance by increasing oxygen consumption, anaerobic threshold and ventilatory efficiency. ET obtains these results by different mechanisms of action. Among ET actions, the modulation of neurohormonal and inflammatory response, the improvement of endothelial function and skeletal muscle mass and metabolism, the preservation of cardiac structure and function through anti-remodeling effects have been well documented. The ET-mediated improvement of exercise tolerance translates in a better mood and quality of life of patients. Despite these important benefits, the real impact of ET on mortality and hospitalization of HFrEF subjects still remains to be clarified. Promising data are today available for different exercise modalities such as RT and hydrotherapy but further long term trials are needed in order to establish their role in CHF treatment. Similarly, only few studies have investigated the effects of ET on HFpEF and up to now several questions on this group of patients still remain unanswered.

CONFLICT OF INTEREST

There are no conflicts of interest with regard to the present study.

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