# Exercise training modalities in chronic heart failure: does high intensity aerobic interval training make the difference?

**Francesco Giallauria[1], Neil Andrew Smart[2], Antonio Cittadini[1], Carlo Vigorito[1]**

*[1] Department of Translational Medical Sciences, Division of Internal Medicine and Cardiac Rehabilitation, Federico II University of Naples, Italy*
*[2] School of Science and Technology, University of New England, Armidale, Australia*

## Abstract

Exercise training (ET) is strongly recommended in patients with chronic heart failure (CHF). Moderate-intensity aerobic continuous ET is the best established training modality in CHF patients. In the last decade, however, high-intensity interval exercise training (HIIT) has aroused considerable interest in cardiac rehabilitation community. Basically, HIIT consists of repeated bouts of high-intensity exercise alternated with recovery periods. In CHF patients, HIIT exerts larger improvements in exercise capacity compared to moderate-continuous ET. These results are intriguing, mostly considering that better functional capacity translates into an improvement of symptoms and quality of life. Notably, HIIT did not reveal major safety issues; although CHF patients should be clinically stable, have had recent exposure to at least regular moderate-intensity exercise, and appropriate supervision and monitoring during and after the exercise session are mandatory. The impact of HIIT on cardiac dimensions and function and on endothelial function remains uncertain. HIIT should not replace other training modalities in heart failure but should rather complement them. Combining and tailoring different ET modalities according to each patient's baseline clinical characteristics (*i.e.* exercise capacity, personal needs, preferences and goals) seem the most astute approach to exercise prescription.

Corresponding author: Francesco Giallauria, Department of Translational Medical Sciences, Division of Internal Medicine and Cardiac Rehabilitation, Federico II University of Naples, Italy.
E-mail: giallauriafrancesco@gmail.com

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## Introduction

The heart failure (HF) syndrome is a steeper growing epidemic that causes a significant socio-economic burden, with its prevalence that reaches up to 10% among persons aged 70 years or older [1]. Despite considerable progress in the pharmacological management of CHF patients, mortality and morbidity still remain a major healthcare concern [2], and frequent hospital admissions have a negative impact on daily life and social activities.

European guidelines for the diagnosis and treatment of acute and chronic HF have incorporated a class IA recommendation for regular aerobic exercise in HF patients to improve functional capacity and symptoms [3]. The current therapeutic strategy, consisting of a titrated drug regimen and innovative electrical implantable devices [4,5], still fails to exert improvement of exercise tolerance. Exercise training (ET) specifically targets this drawback and is considered one of the most effective interventions to improve patients' health status perception.

## Pathophysiological effects of exercise training

Exercise capacity depends on central cardiac, as well as peripheral mechanisms. The correlation between peak oxygen consumption ($VO_2$peak) and resting left ventricular ejection fraction (LVEF) is poor in patients with chronic heart failure (CHF) [6,7]. Therefore, cardiac reserve during exercise, as well as peripheral vascular function, oxygen uptake and utilization (skeletal muscle), increased ergoreceptor activity and ventilatory inefficiency shoud be accounted for [8,9].

In CHF patients, ET decreases circulating catecholamine levels [10,11], has anti-inflammatory [12,13] and antioxidative effects [14], reduces natriuretic peptide concentrations [15-18], exerting a reduction in peripheral vasoconstriction, an improvement of endothelial function and endothelial repair enhancement [9,19]. Regular ET also prevents muscle wasting and restores the anabolic/catabolic imbalance [20], as well as hyperactive muscle ergoreflexes [8,9]. These changes parallel observed training-induced increases in $VO_2$peak.

## Impact of exercise training on mortality

The ExTraMATCH (Exercise Training for Chronic Heart Failure) collaborative group, analysing 9 randomized controlled clinical trials (RCTs) (801 patients), calculated 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 favour of ET [21]). Another meta-analysis including 11 RCTs (729 patients) and found a 39% lower relative risk for mortality in the exercise group [22]. However, none of the studies included in these meta-analyses had sufficient power to address hard endpoints. In addition, most of them were small single-centre trials. The recent HF-ACTION trial (Heart Failure - A Controlled Trial Investigating Outcomes of exercise TraiNing) is the largest multicentre RCT (2331 patients) designed to measure the effects of exercise training on clinical outcomes and safety in patients with stable systolic HF [23]. After a median follow-up time of 30 months, and after adjustment for predefined prognostic predictors, all-cause mortality or all-cause hospital stay was significantly reduced (-11%, p=0.03) in the training group. The major study flaw, however, was the very low level of adherence to the prescribed exercise regimens, resulting in a smaller than expected improvement in aerobic capacity. This aspect pointed out the needing of delineating new stretegies for improving adherence to exercise-based cardiac rehabilitation programs.

## Prescription of a training programme

Along with lifestyle changes, HF guidelines recommend stable HF patients undergoing structured ET programme [24,25].

Since the lack of clearly delineated practical guidelines for ET prescription in the setting of HF, a variety of centre-specific approaches for these patients have been proposed [26]. The programmes may differ in several aspects: type (endurance, resistance and strength), intensity (aerobic *versus* anaerobic); method (continuous versus intermittent/interval); setting (hospital/centre-based *versus* home-based); application (systemic, regional and respiratory muscle) and control (supervised *versus* nonsupervised) [26].

## Aerobic or endurance exercise training

Aerobic or endurance training (*i.e*., cycling, walking, rowing) is the most investigated ET modality in CHF patients, and is recommended as baseline activity [21,22,24,25,27,28]. Cycling is usually preferred because of the reproducible power output and reduced injury rate, and allow to exercise at low workloads.

To avoid exercise-related risks and adverse events, traditionally, the maximum training intensity for HF patients is identified at the first ventilatory anaerobic threshold (VAT) (50-60% of $VO_2$peak) [29,30]. However, since CHF patients need higher percentage of their $VO_2$peak (compared with normal individuals) to perform daily life activities [31-33], and since one of the main objectives of ET is allowing these patients to perform daily tasks with less effort, training intensities above the VAT have progressively been tested and introduced.

The respiratory compensation point (RCP) (65-90% of $VO_2$peak) [34], which is the limit between high intensity and severe intensity of effort (also named 'critical power'), is now accepted as the limit for prolonged aerobic exercise without exposing to additional risk CHF patients [35,36]. Nowadays, ET intensities between 70-80% of $VO_2$peak are commonly prescribed [37,38]. Nevertheless, in CHF patients with significantly lower pretraining $VO_2$ peak and/or high exercise-related risks (more compromized patients), aerobic training intensities as low as 40% of $VO_2$peak have proven to be effective [39]. It should be reminded that indoor workloads cannot reliably be extrapolated to outdoor exercise, since environmental conditions can magnify the exercise workload, potentially increasing risks.

## High intensity interval training

The concept of interval training (HIIT) was developed across several decades [40,41], and was first used by athletes who trained at velocities close to their specific competition velocity. HIIT was based on the possibility of intensifying the action of the trianig upon the body throughtout the increase on exercise intensity and decrease on exercise duration (short bouts of high intensity exercise) interspersed by short periods of rest or low-intensity exercise. The rationale behind HIIT is that the total amount of high-intensity exercise is higher than could be attained during a single bout of continuos exercise at the same intensity until to their maximum or even supra-maximum effort, the active recovery could be better.

Meyer *et al.* [42] performed the first HIIT study in CHF patients. These authors compared the effects of 3-week HIIT versus activity restriction in 18 patients with severe CHF (mean LVEF 21±1%, mean $VO_2$ peak 12.2±0.7 mL/kg/min). The HIIT protocol consisted of 30/60 second work/recovery intervals at respectively 50% of maximal short-term exercise capacity and 15 watts, during 15 min, 5 times/week. These Authors reported a 24% increase in $VO_2$ peak [42] and a 6.5% improvement in 6-min walk test [43] in the HIIT group.

Since then, several small single-center RCTs comparing HIIT to moderate-intensity continous ET have been performed [44-53]. In 2007, Wisloff and colleagues [44] compared the effect of HIIT, consisting of 4-min training intervals at high intensity (90-95% of peak heart rate), separated by 3-min active pauses (walking at 50-70% of peak heart rate), total exercise time 38 min, three times weekly, with moderate-intensity continuous ET, which consisted of walking continuously at 70-75% of peak heart rate, for 47 min (to compare isocaloric sessions). The study population consisted of 27 postinfarction HF patients aged 75±11 years and with mean LVEF of 29%. The investigators reported that HIIT led to greater improvements in aerobic capacity (improvement in $VO_2$ peak 46% *vs* 14%, $p<0.001$), reverse left ventricular remodelling, endothelial function and QoL. These impressive findings have generated a wave of enthusiasms in the cardiac rehabilitation community. Subsequently, several other groups have demonstrated the benefits of HIIT in CHF patients [45-53]. Using a similar protocol with 3/3 minutes work/recovery intervals at respectively 80% and 40% of peak power output, Wang *et al.* (50) demonstrated a 23% increase in $VO_2$ peak in the HIIT group compared to non significant changes in the moderate-countinous ET group [$p<0.05$]. Ventilatory efficiency and cardiac output were also significantly increased in the HIIT group compared to moderate-countinous ET group. Comparable improvements in $VO_2$ peak (respectively 21% and 13% in the HIIT and moderate-continous ET groups) were observed by Smart *et al.* [45] after 16 weeks of stationary cycling thrice a week. Notably, no significant changes in left ventricular dimensions or systo-diastolic function were detected [45]. A peculiarity of this study was that HIIT and moderate-countinous ET protocols only differed by the addition of 60 seconds of rest each minute in the HIIT group, and otherwise used the same moderate intensity (70% of $VO_2$peak) for exercise intervals [45]. Finally, in a short but intensive intervention (6 times/week during 8 weeks), Freyssin *et al*. demonstrated $VO_2$ peak increase of 22% compared to 2% only in the moderate-countinous ET group [48].

A meta-analysis including CHF patients by Haykowsky *et al.* [54] showed higher increase in $VO_2$peak with HIIT [HIIT *vs* moderate continous ET, weighted mean difference (WMD) 2.14 mL $O_2$/kg/min, 95% confidence interval (95% CI) 0.66 to 3.63], reiforcing these findings. The 5 RCTs meta-analyzed included clinically stable patients with CHF with reduced ejection fraction with impaired left ventricular systolic function (mean LVEF 32%) who were relatively young (mean age 61 years) and predominantly men (82%) [44]. Comparison of the effects of HIIT and moderate continous ET on the resting LVEF was inconclusive [HIIT *vs* moderate continous ET, WMD 3.29%, 95% CI -0.7% to 7.28%].

A more recent meta-analysis by Smart *et al.* [55] analyzed 446 patients: 212 completed HIIT, 66 only continuous ET, 59 completed combined HIIT and strength training and 109 sedentary controls. Compared to continous ET, HIIT determined a significant increase in $VO_2$peak [WMD 1.04 mL/kg/min, 95%CI 0.42 to 1.66, p=0.0009], respectively. Interestingly, HIIT and strengt training (combined) determined a superior effect on $VO_2$ peak compared to HIIT alone [WMD -1.10 mL/kg/min, 95%CI -1.83 to -0.37, p=0.003]. Moreover, in studies reporting VE/VCO2slope, HIIT improved ventilatory efficiency *vs* controls [HIIT *vs* control groups, WMD -1.50, 95%CI -2.64 to -0.37, p=0.01]; and *vs* continuous ET [WMD -1.35, 95%CI - 2.15 to -0.55, p=0.001].

Hovewer, not all studies have systematically demonstrated the superiority of HIIT over moderate-countinous ET in improving cardiopulmonary functional capacity. Using an exercise protocol with 30/30 seconds work/recovery intervals at high intensity (100% of peak power output) and passive recovery, Dimopoulos *et al.* [46] only reported a modest increase in $VO_2$peak in the HIIT group compared to moderate-countinous ET group, without significant differences between groups (8% *vs* 6%, respectively) [45]. Moreover, these authors reported a significant increase in heart rate recovery only in the moderate-countinous ET group suggesting a positive exercise-induced effect on autonomic function modulation [45]. These findings were in line with previous studies in post-infarction patients demonstrating a significant improvement in heart rate recovery after 3 to 6 months moderate-countinous ET programs [56-58].

Recently, a very similar exercise intervention as described by Wisloff *et al.* [44] but with slightly lower intensities, Iellamo *et al.* [51] reported a 22% improvement in $VO_2$peak in both HIIT and moderate-countinous ET groups, while neither training modality influences left ventricular remodelling indexes or cardiac output [51]. More recently, the same research group investigated the exercise-induced hormonal response in patients with CHF [59]. These Authors found that, although both ET modalities exerted the same improvement in $VO_2$peak, HIIT resulted in a greated exercise-induced anabolic response; thus suggesting that the amoung of hormonal response is related to the exercise intensity [59]. Similar results have been previously documented in healthy subjects in which the greated hormonal response has been ascribed to the higher mechanical and metabolic stimuli induced by HIIT [60].

A randomized multicentre trial (SMARTEX-HF study) is currently recruiting HF patients in order to compare the efficacy and safety of HIIT *versus* continous aerobic ET [61]. The results of this trial are eagerly awaited since they are expected to provide a more solid basis for future recommendations on training modalities.

Recently, data on safety of HIIT in cardiac patients (however not exclusively HF patients) [62] reported that the risk of a cardiovascular event is even lower after both HIIT and moderate-intensity ET in cardiovascular rehabilitation setting [62]. More recently, Levinger *et al.* [63] performed a systematic review to evaluate the safety of acute HIIT in patients with cardiometabolic diseases. Authors found that the incidence of adverse responses during or within 24 h post-HIIT in patients with cardiometabolic diseases is around 8%, which is somewhat higher compared to the previously reported risk during moderate-continuous ET [63]. These findings suggest that patients who wish to perform HIIT should be clinically stable, have had recent exposure to at least regular moderate-intensity exercise, and appropriate supervision and monitoring during and after the exercise session are mandatory [63].

## Conclusions

In patients with CHF, mounting evidence suggests that HIIT exerts larger improvements in cardiopulmonary functional capacity compared to moderate-continuous ET. These results are intriguing, mostly considering that better functional capacity translates into an improvement of symptoms and QoL. In addition, HIIT studies performed in selected CHF cohorts did not reveal major safety issues; although patients should be clinically stable, have had recent exposure to at least regular moderate-intensity exercise, and appropriate supervision and monitoring during and after the exercise session are mandatory. Conversely, the impact on cardiac dimensions and function and on endothelial function remains uncertain. Differences in results may be ascribed to differences in patient characteristics and/or in training protocols. In fact, it is currently uncertain whether a specific HIIT protocol is superior to another. Furthermore, all studies were single-center, and, in the vast majority, investigators were not blinded to outcome assessments, which surely represent limitations.

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