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Exercise training in patients with chronic heart failure: A new challenge for Cardiac Rehabilitation Community

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Abstract

Exercise training (ET) is strongly recommended in patients with chronic stable heart failure (HF). Moderate-intensity aerobic continuous ET is the best-established training modality in HF patients. In the last decade, however, high-intensity interval exercise training (HIIT) has aroused considerable interest in cardiac rehabilitation community. In HF patients, HIIT exerts larger improvements in exercise capacity compared to moderate-continuous ET. Since better functional capacity translates into symptoms relief and improvement in quality of life in patients with HF, this training modality is collecting growing interest and consensus, not revealing major safety issues. HIIT should not replace other training modalities in HF but should rather complement them. Inspiratory muscle training, another promising training modality in patients with HF, exerts beneficial effect on inspiratory muscle strength and inspiratory endurance, on exercise capacity and quality of life. In conclusion, taking into consideration the complecity of HF syndrome, combining and tailoring different ET modalities according to each patient's baseline clinical characteristics (*i.e.*, exercise capacity, comorbidity, frailty status, personal needs, preferences and goals) seem the wiliest approach for exercise prescription. The present review aims at discussing the rececent evidences on the effects of exercise training in patients with chronic HF (with both reduced and preserved left ventricular function).

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Introduction

Heart failure (HF) is an exponentially growing epidemic syndrome leading to significant socio-economic burden, with a prevalence that reaches up to 10% among persons aged 70 years or older [1]. Despite impressive advances in the pharmacological treatment of HF, mortality and morbidity still remain a major concern [2], and frequent hospital admissions have a deleterious impact on daily life and social activities. European guidelines have incorporated a class IA recommendation for regular aerobic exercise in HF patients to improve functional capacity and symptoms relief [3-5]. Mechanisms underlying exercise-induced improvement in exercise tolerance are summarized in Table 1. Notably, the current therapeutic strategy, based on a titrated drug regimen and innovative electrical implantable devices still fails to ameliorate exercise tolerance [6,7]. Exercise training (ET) is considered one of the most effective interventions to improve cardiopulmonary functional capacity and patients' health status perception in patients with HF (either with reduced or preserved left ventricular ejection fraction) [3,5,8-16]. In people with both systolic HF and HF with preserved left ventriculr ejection fraction (HFpEF), cardiorespiratory fitness is impaired. Impaired peak oxygen consumption (peakVO2) has been associated with increased mortality risk [17] and decreased quality of life in patients with HF. In addition, by using traditional echocardiograhic indices of measurement (left ventricular ejection fraction), systolic function appears largely normal under resting conditions in HFpEF. However, studies have shown through global assessment of systolic function by strain rate imaging, systolic abnormalities do exist in HFpEF patients [18]. Despite the preservation of resting systolic function, mortality rates in HFpEF are similar to those observed in systolic failure [19]. Apart from HF, ET efficacy is under active investigation in a wide range of cardiovascular, endocrine, and neurological disorders ranging from pulmonary hypertension, to Friedereich's ataxia, conditions of GH excess and deficiency, and Takotsubo cardiomyopathy [20-28].

The present review aims at discussing the rececent evidences on the effects of exercise training in patients with chronic HF (with both reduced and preserved left ventricular function).

Pathophysiological effects of exercise training

Exercise capacity depends on central cardiac, as well as peripheral mechanisms [29,30]. In fact, the correlation between peak oxygen consumption (VO_2peak) and resting left ventricular ejection fraction (LVEF) is scarce in patients with HF. Therefore, cardiac reserve during

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exercise, together with peripheral vascular function, oxygen uptake and utilization (skeletal muscle), increased ergoreceptor activity; but ventilatory inefficiency should be accounted for [31,32].

In patients with HF, ET decreases circulating catecholamine levels [33,34], has anti-inflammatory [35,36] and antioxidative effects [37,38] reduces natriuretic peptide leves [39-42], exerting a reduction in peripheral vasoconstriction, an improvement of endothelial function and endothelial repair enhancement [32,43-45]. Regular ET also prevents muscle wasting and restores anabolic/catabolic imbalance [46-48], as well as hyperactive muscle ergoreflexes [31,32]. These changes parallel observed training-induced increases in VO_2peak and exert beneficial effects on clinical outcomes [49].

In patients with HFpHF, recent meta-analysis showed a significant improvement in peakVO2 of 2.13 ml/kg/min [95% confidence interval (CI) 1.54 to 2.71, P<0.00001] in exercise *vs* control [16]. These data are in line with previous meta-analysis with a similar effect size seen previously [50]. Interestingly, the meta-analysis by Dieberg *et al.* [16] is the first to identify that exercise training may significantly improve diastolic function as evaluated by E/A ratio. Neither individual studies, nor pooled analyses published previously, have shown a post-exercise training benefit [50]. Moreover, this meta-analysis showed an exercise-induced improvement (small reduction) of E/E' which is a surrogate of filling pressure. Finally, the same meta-analysis [16] showed a significant reduction in deceleration time (DT). Taken together, these three measures of diastolic function have shown a trend toward normalization after ET. While exercise-induced improvement of diastolic function has been previously demonstrated in healthy people [51], previous work in HFpEF has failed to show a trend toward improved E/A and DT [52]. Further well-designed and appropriately powered studies on HFpEF cohort are required to provide evidence on the pathophysiological effects of ET on diastolic function improvement.

Impact of exercise training on mortality

Exercise training results in 35% lower risk for mortality and in 28% lower risk for the composite endpoint of mortality or hospitalization in the ExTraMATCH (Exercise Training for Chronic Heart Failure) collaborative group [53]. Another meta-analysis including 11 randomized controlled studies (RCTs) found a 39% lower relative risk for mortality

Table 1. Pathophysiological mechanisms underlying exercise-induced improvement in exercise tolerance.

Brain
↑Arterial baroreflex sensitivity/control
↑Sympathoexcitation/vasoconstriction (gut/muscle/skin/general)
Arteries
↑Sympathovagal balance (↓resting heart rate, ↑heart rate recovery)
↑Systemic arterial compliance, ↑CPCs, ↑Endothelium-mediated vasodilation, ↑NO bioavailability, ↑tetraidrobiopterine (BH_4), ↓ROS, ↓Catecholamines,↓Endothelin-1, ↓Angiotensin II, ↓Arginine-vasopressin,↓BNP, ↓NT-proBNP, ↓Circulating cytokines
Inflammatory markers
↓TNF-, ↓IL-1β ↓IL-6 (background and phasic), ↑IL-10, IIra, Soluble TNF receptors I and II, ↓C-reactive protein, ↓adhesion molecules *[Overall, exercise training exerts antinflammatory effect)*
Lung
↓Vascular pressure/↓ventilation/perfusion mismatch
↓Stiffness/↑Diffusion capacity
↓Pulmonary artery resistance/pressure
↓Alveolar-arterial O_2 gradient
Respiratory muscle: ↓Blood Flow, ↓VO_2
Kidney
↓Sympathoexcitation/vasoconstriction
Heart
↓LV remodelling, LV size, LVEDP
↑Ejection fraction, Stroke Volume, Maximal cardiac output, Endothelium-mediated coronary dilation
↓Total peripheral resistance
Muscle
↑Blood flow, Capillaries per fiber, Mitochondrial volume/oxidative enzyme activity, O_2 diffusing capacity, O_2 delivery-VO_2 matching, NO availability and Endothelium-mediated vasodilation, Apoptosis/atrophy, Muscle pump
↓iNOS, Vascular stiffness, metaboreflex
↓
All these changes contribute to increase speed VO_2 kinetics (↑VO_2max, Critical Power, Lactate Threshold,↓O_2 cost of exercise
↓
↑ EXERCISE TOLERANCE

BNP, brain natriuretic peptide; CPCs, circulating progenitor cells; HR, heart rate; LVEDP, left ventricular (LV) end-diastolic pressure; iNOS, inducible nitric oxide (NO) synthase; NO, nitric oxide; ROS, reactive oxygen species; VO_2max, maximum oxygen consumption.

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in the exercise group [54]. However, none of the RCTs included in these meta-analyses had sufficient power to address hard endpoints; and most of them were small single-centre trials. The HF-ACTION trial (Heart Failure - A Controlled Trial Investigating Outcomes of exercise TraiNing) is the largest recent multicentre RCT designed to measure the effects of exercise training on clinical outcomes and safety in patients with HF [55]. After a median follow-up time of 30 months, and after adjustment for predefined prognostic predictors, all-cause mortality or all-cause hospital stay were significantly reduced (-11%, p=0.03) in the training group. However, this trial was biased by a very low adherence level to exercise prescription regimen, resulting in a smaller than expected improvement in aerobic functional capacity. This issue reinforces the need for delineating new stretegies aimed at improving adherence to exercise-based cardiac rehabilitation programs [56,57].

Exercise prescription

The lack of clearly delineated practical guidelines for ET prescription determined a variety of centre-specific approaches for HF patients [58]. The exercise programmes may differ in terms of type (endurance, resistance and strength), intensity (aerobic *vs* anaerobic); method (continuous *vs* intermittent/interval); setting (hospital/centre-based *vs* home-based); application (systemic, regional and respiratory muscle) and control (supervised *vs* nonsupervised) [58].

Aerobic or endurance exercise training

Aerobic or endurance training (*i.e.*, cycling, walking, rowing) is the most adopted modality in patients with HF, and is recommended as baseline activity [53,54,58-60]. Cycling is usually preferred because of the reproducible power output and reduced injury rate, and allow to exercise at low workloads.

In order to avoid exercise-related risks and adverse events, the maximum training intensity for HF patients is usually identified at the first ventilatory anaerobic threshold (VAT) (50-60% of VO_2peak) [61,62]. However, taking into consideration that patients with HF need higher percentage of their VO_2peak (compared to normal subjects) to perform daily life activities [63-65], and since one of the main scopes 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 (65-90% of VO_2peak) [66], which is the limit between high-intensity and severe-intensity effort ("critical power"), is now recognized as the limit for prolonged aerobic exercise without exposing to additional risk HF patients [67,68]. Currently, exercise intensities between 70-80% of VO_2peak are commonly prescribed [69,70]. Nevertheless, in HF patients with significantly lower pre-training VO_2peak and/or high exercise-related risks (more compromised and deconditioned patients), aerobic training intensities as low as 40% of VO_2peak have proven to be effective and safe [71].

High intensity interval training

The concept of high intensity interval training (HIIT) was developed across several decades [72,73]. Basically, HIIT was conceived on the possibility of intensifying the action of the traning throughtout the increase on exercise intensity and decrease on exercise duration (short bouts of high intensity exercise) interpolated 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 [72,73].

About 20 years ago, Meyer *et al.* [74] compared the effects of 3-week HIIT *vs* activity restriction in 18 patients with severe HF. 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 minuts, 5 times/week. Authors reported 24% increase in VO_2peak [74] and a 6.5% improvement in 6-minute walk test distance [75] in the HIIT group.

Since then, a number of small single-center RCTs comparing HIIT to moderate-intensity continous ET have been performed [76-85]. In 2007, Wisloff *et al.* [76] compared the effect of HIIT [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 per week], with moderate-intensity continuous ET [walking continuously at 70-75% of peak heart rate, for 47 min]. In a cohort of 27 post ischemic HF patients aged 75±11 years and with mean LVEF of 29%, the Authors observed that HIIT led to greater improvements in aerobic capacity (VO_2peak increase of 46% *vs.* 14% in HIIT group, p<0.001), reverse left ventricular remodelling, endothelial function and quality of life. These impressive findings have generated a wave of enthusiasm among the cardiac rehabilitation community. In addition, other studies reported the benefits of HIIT in HF patients [77-95]. Using similar protocols (3/3 minutes work/recovery intervals at respectively 80% and 40% of peak power output), Wang *et al.* [75] 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. After 16 weeks of stationary bike three times/week, Smart *et al.* [77] described comparable improvements in VO_2 peak (respectively 21% and 13% in the HIIT and moderate-countinous ET groups). Of note, no significant changes in left ventricular dimensions or systolic/diastolic function were detected [77]. Finally, in shorter but intensive intervention (6 times/week during 8-week program), Freyssin *et al.* demonstrated 22% of VO_2 peak increase compared to only 2% increase in the moderate-countinous ET group [80].

Data from meta-analysis including patients with HF showed higher HIIT-induced increase in VO_2 peak compared to other training modalities [86]. The 5 RCTs meta-analyzed included clinically stable patients with HF with reduced ejection fraction (mean LVEF 32%), relatively young (mean age 61 years) and predominantly men (82%) [79]. Of note, comparison of the effects of both HIIT and moderate continous ET on resting LVEF was inconclusive [86].

Smart *et al.* [87] analyzed a cohort of 446 patients: 212 completed HIIT, 66 only continuous ET, 59 completed combined HIIT and strength training and 109 sedentary controls. Compared to continous training, HIIT determined a significant increase in VO_2peak [87]. Interestingly, HIIT and strength training (combined) determined a superior effect on VO_2 peak compared to HIIT alone [87]. In addition, in selected studies, HIIT improved ventilatory efficiency compared to controls or continous training [87].

A more recent meta-analysis reported significant improvements in peak VO_2 after HIIT in HF patients [88]. Interestingly, in HF patients, there were no improvements when the intensity recovery was ≤ 40% of VO_2 peak and the frequency of training was ≤ 2 days/week. In addition, in HF patients, programs lasting <12 weeks did not significantly improve VO_2peak. These data support the needing of long-term exercise-based cardiac rehabilitation programs [89].

Hovewer, the superiority of HIIT over moderate-countinous training in improving cardiopulmonary functional capacity was not systemati-

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cally ascertained. 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.* [78] reported a quite modest increase in VO_2 peak in HIIT cohort compared to moderate-countinous training group [78]. Notably, a significant increase in heart rate recovery was exclusively reported in the moderate-countinous ET cohort suggesting a positive exercise-induced effect on autonomic function modulation [76]. 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 [90-92].

Recently, by using a similar exercise intervention as described by Wisloff *et al.* [76] but with slightly lower intensities, Iellamo *et al.* [83] reported a 22% improvement in VO_2peak in both HIIT and moderate-countinous ET cohorts, while neither training modality influences left ventricular remodelling indexes or cardiac output. The same research team investigated the exercise-induced hormonal response in patients with HF founding that, although both training modalities had the same effect on VO2peak, HIIT resulted in a greated exercise-induced anabolic response; hence, suggesting that the amount of hormonal response is related to the exercise intensity [83]. Similar results have been previously documented in healthy subjects in which the greater hormonal response has been ascribed to the higher mechanical and metabolic stimuli induced by HIIT [93,94].

The SMARTEX-HF study, a randomized multicentre trial, is currently recruiting HF patients comparing the efficacy and safety of HIIT *versus* continous aerobic ET [95]. The results of this trial are eagerly awaited since they are expected to provide a more solid basis for future recommendations on training modalities.

Reported data on safety of HIIT in cardiac patients (however not exclusively HF patients) showed that the risk of a cardiovascular event is even lower after both HIIT and moderate-intensity ET in cardiovascular rehabilitation setting [96], even after acute decompensation [97]. A recent systematic review evaluating the safety of acute HIIT in patients with cardiometabolic diseases reported that the incidence of adverse responses during or within 24-hours after HIIT in patients with cardiometabolic diseases is around 8%, which is slightly higher compared to the previously reported risk during moderate-continuous ET [98]. These findings indicate 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 [98].

Inspiratory muscle training

In patients with HF, inspiratory muscle weakness and peripheral skeletal muscle dysfunction may underlie fatigue, dyspnea, and exercise intolerance. Structural and biochemical alterations of the diaphragm muscle have been reported, including increased proportion of type I fibers, reduced type IIb fibers, and fiber atrophy due to chronic increase in diaphragm load and systemic myopathy [99-101].

Inspiratory muscle strength is assessed by maximal inspiratory pressure (PImax). It is measured at the mouth level by asking the subject taking a maximal inspiration while at residual volume and sustained for at least one second. According to the force-length relationship, the higher the position of the diaphragm (the longer the resting length of the diaphragm, or the lower the lung volume), the higher the PImax. This measure is independent of the patient's respiratory flow and is highly reproducible.

In patients with HF, PImax lower than 70% of the predicted value indicates respiratory muscle weakness [102]. Inspiratory muscle endurance refers to the ability to sustain a certain respiratory pressure over time which can be measured asking the subject to sustain the PImax over time in order to obtain the sustained maximal inspiratory pressure [103-105]; otherwise measuring the highest pressure that the subject can maintain for at least one minute (Pth max) [102].

Inspiratory muscle training is beneficial for patients with HF. The benefits include increased inspiratory muscle strength, increased inspiratory endurance, improved exercise capacity, reduced dyspnea, and improved quality of life. The effect sizes were considered adequate for improvements of respiratory muscle strength, functional exercise capacity, and reduction of dyspnea [106,107].

Of great interest is the 'aerobic/resistance/inspiratory (ARIS) muscle training hypothesis in HF, which is based on the decoding of the 'skeletal muscle hypothesis in HF' and on revision of experimental evidence showing that exercise and functional impairment in HF patients are not only associated with reduced muscle endurance, a clear indication for aerobic training; but also with reduced muscle strength and impaired inspiratory muscle function leading to dyspnea, fatigue, weakness, and low aerobic capacity, at the basis of the indication for adding both resistance and inspiratory muscle training to aerobic training [108]. Lautaris postulated that combined ARIS muscle training might result in maximal exercise pathophysiological and functional benefits in patients with HF [108]. The hypothesis will be tested by comparing all potential exercise combinations, ARIS, aerobic *vs* resistance training, aerobic *vs* inspiratory muscle training, aerobic training alone, evaluating both functional and cardiac indices in a large sample of HF patients (Aerobic Resistance, InSpiratory Training OutcomeS in Heart Failure, ARISTOS-HF trial).

Conclusions

In patients with HF, exercise training exerts large improvements in cardiopulmonary capacity, mostly when different training modalities are combined. Since better functional capacity always translates into symptoms relief and QoL improvement, these results are intriguing for cardiac rehabilitation community. Further studies should be designed in order to establish the best strategy in terms of type, duration, frequency and intensity of ET programs. A demanding challenge will be translating these protocols to HF patients with relevant comorbidity (*i.e.*, frailty), after cardiac surgery or with advanced age.

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