Review

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Implementation of Exercise Training to Improve Outcomes in Patients with Heart Failure

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Implementation of Exercise Training to Improve Outcomes in Patients with Heart Failure

Loay Eleyan [1,*], Ahmed R Gonnah [2,*], Imran Farhad [3,*], Aser Labib [4], Alisha Varia [3], Alaa Eleyan [5], Abdullah Almehandi [6], Abdulrahman O Alnaseem [7] and David H Roberts [3,8,*]

[1] Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom
[2] Imperial College Healthcare NHS Trust, London, United Kingdom
[3] School of Medicine, University of Liverpool, Liverpool, United Kingdom
[4] Sheffield Teaching Hospitals NHS Trust, Sheffield, United Kingdom
[5] SchoolofMedicine,UniversityofManchester,Manchester,UnitedKingdom
[6] Institute of Cardiovascular Sciences, University College London, London, United Kingdom
[7] Department of Surgery, Jaber Al-Ahmad Hospital, Kuwait
[8] Lancashire Cardiac Centre, Blackpool, United Kingdom
* Correspondence: loayeleyan@gmail.com (L.E.); ahmedgonnah18@outlook.com (A.R.G.); hlifarha@liverpool.ac.uk (I.F.); d.h.roberts@liverpool.ac.uk (D.H.R.)

Abstract: Heart Failure (HF) is a prevalent condition which places a substantial burden on healthcare systems worldwide. Pharmacological therapy structures the cornerstone of management in HF reduced ejection fraction (HFrEF), including angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor-neprilysin inhibitors (ARNI), beta blockers (BB), mineralocorticoid receptor antagonists (MRA) and sodium/glucose co-transporter 2 (SGLT2) inhibitors, which all improve survival rates. Mortality reduction with pharmacological treatments in HF preserved ejection fraction (HFpEF) are yet to be established. Cardiac rehabilitation and exercise training can play an important role in both HFrEF and HFpEF. Cardiac rehabilitation significantly improves functional capacity, exercise duration and quality of life. Exercise training has shown beneficial effects on peak oxygen consumption (pVO2) and 6-minute walk test distance in HFrEF and HFpEF patients as well as a reduction in hospitalisation and mortality rates. ET also has been shown to have beneficial effects on depression and anxiety levels. High intensity training and moderate continuous training have both shown benefit, while resistance exercise training and ventilatory assistance may also be beneficial. ET adherence rates are higher when enrolled to a supervised programme but prescription rates remain low worldwide. Further research is required to establish the most efficacious exercise prescriptions in patients with HFrEF and HFpEF, but personalised exercise regimens should be considered as part of HF management.

Keywords: Exercise training; HFpEF; HFrEF; pVO2; 6-minute walk test

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Introduction

Heart failure (HF) is a multifaceted and prevalent condition, affecting over 64 million individuals worldwide and standing as a leading cause of hospitalisation and mortality, thus posing a significant public health challenge [1]. Its prevalence ranges from 1-2%, with a notable increase in the older population, surpassing 10% among those aged 70 and above [2,3]. HF ESC classification is usually based on ejection fraction (EF): preserved, >50% (HFpEF), mid-range, 41-49% (HFmrEF), reduced, <40% (HFrEF), and improved, 10-point increase from baseline with a subsequent ejection fraction exceeding 40% (HFImpEF) [4–6]. Women generally having a higher incidence of HFpEF. Developed countries have witnessed a decline in the incidence of HFpEF and HFrEF, primarily attributed to advancements in HF management, with HFrEF showing a more significant decrease (-45%) compared to HFpEF (-28%) [7].

This review highlights the emerging role of exercise training (ET) for treating chronic heart failure patients with HFpEF and HFrEF.

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Pathophysiology

Sarcopenia is found in 20-50% of HFrEF patients and contributes directly to frailty, exercise intolerance, and early fatigue. It poses a significant impact on daily activities, and is associated with an increased morbidity and mortality [8–10]. HFrEF patients have more pronounced molecular alterations within skeletal myocytes including a shift in muscle fibre type from slow to fast twitch fibres (type I to type IIb) [11]. This could be due to the reduction of PGC-1α (peroxisome proliferator-activated receptor gamma coactivatory-1 alpha), a key regulator for type 1 fibre formation [12]. A decrease in the number of capillaries per fibre is also seen in both HFrEF and HFpEF patients, implying a less efficient system of diffusion from blood to myocyte [11]. HFrEF and HFpEF have both been linked with rapid depletion of high-energy phosphate as well as impairment in mitochondrial oxidative capacities [11]. Contribution of all these factors as well as the presence of a systemic inflammatory response, leads to muscle atrophy ,exercise intolerance and a decrease in quality of life [11]. An overview of the musculoskeletal changes in HF has been visualised in Figure 1.

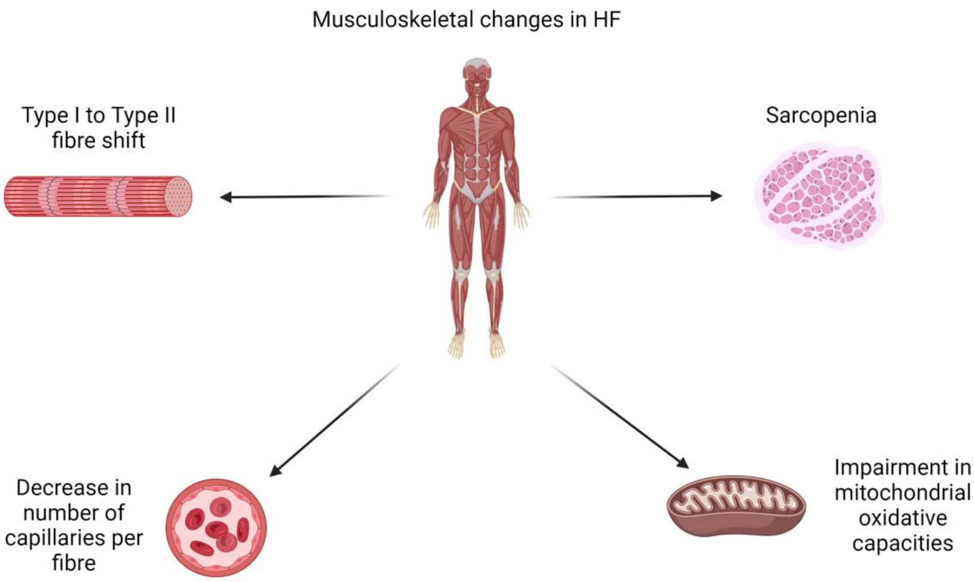

Figure 1. [Musculoskeletal changes in HF].

Functional Assessment in Heart Failure

The New York Heart Association (NYHA) classification helps gauge the clinical status of HF patients but functional capacity assessment helps to determine exercise tolerance. Peak oxygen consumption (VO2) by cardiopulmonary exercise testing (CPET) is generally considered the best indicator for endurance and fitness and is associated with indices of health-related quality of life (HRQoL) [13]. Abnormal CPET have been shown in both HFpEF and HFrEF patients, with HFrEF patients exhibiting relatively low peak oxygen uptake (pVO2) and elevated VE/VCO2 slopes – a sign of poor ventilatory efficiency due to more ventilation requirment to remove a given amount of CO2. [14].

The 6 minute walking test distance (6MWTD) is a simpler and reproducible alternative to CPET and has proven useful in assessing functional capacity and clinical outcomes in HF patients [6,14,15]. Several trials have also reported 6MWTD to evaluate the efficacy of different treatments [16]. The distance walked is associated with improved survival rates at univariate analyses, but not at

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multivariate analyses, which highlights the importance of the consideration of other factors such as peak VO2 and NYHA class [17]. Mortality has been shown to be higher in those who manage to walk <350 meters [18].

HF patients are at increased risk of frailty in comparison to the general population [19,20], which equates to higher hospitalisation rates, longer hospital stays and increased mortality [21–23].Frailty indexes can be used to quantify risks among HF patients using variables such as symptoms, disabilities and laboratory abnormalities [24]. BNP and NT-proBNP play an important role in the diagnosis and monitoring of HF patients [25]. Reductions in these biomarkers following aerobic and/or resistance exercise training is associated with functional improvement in patients with HFrEF and they have been used to objectively to monitor response to cardiac rehabilitation and ET programmes [25].

Optimising Functional Capacity in Heart Failure

Angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor-neprilysin inhibitors (ARNI), beta blockers, mineralocorticoid receptor antagonists (MRA) and sodium-glucose co-transporter 2 (SGLT2) inhibitors all improve survival, alleviate symptoms, reduce hospitalisations and Improve physical function in patients with HFrEF [26–30]. Despite optimal guideline-directed medical therapy (GDMT), there has been a notable increase in the incidence, and prevalence of HF-related hospitalisations [1–3].

Histological examination of skeletal muscle in patients with HF show reduced oxidative capacity, reduced volume density and reduced surface area of mitochondrial cristae caused by insufficient blood flow during exercise [31]. Trials in patients with HFrEF have shown that after treatment with an ACE-I, the inability of peripheral vessels to dilate was reversed, increasing blood flow and in turn improving oxidative capacity and ultimately exercise tolerance [32]. After 6 months of ARNI treatment in patients with HFrEF cardiopulmonary test variables improved; peak VO2 increased from 15.8 ± 3.4 to 17.0 ± 4.0 ml/kg/min and O2 pulse increased from 11.5 ± 2.5 to 12.6 ± 2.4 ml/beat [33]. ARNI treatment also demonstrated reduced Nt-proBNP levels, increased ejection fraction, and improved NYHA class [34]. Similarly, MRA treatment improved exercise capacity in patients with HFrEF [35]. In HFpEF, pharmacological treatments primarily focus on symptom management, (e.g. diuretics for fluid overload) and addressing underlying causes [6,36–38]. MRA appear to have no effect on peak VO2, 6MWD or QoL in HFpEF [24]. Conversely, beta blocker withdrawal in HFpEF exhibited a significant increase in peaks VO2 band peak VO2% compared to controls [39], associated with a significant improvement in QoL [39].

Iron deficiency anaemia is recognised in patients with HFrEF and is associated with reduced exercise capacity [40]. Improvement is seen in pVO2, exercise capacity and QoL following iron infusions [40,41]. Evidence in HFpEF remains uncertain, although improved exercise capacity has been noted, explained by a reduced production of oxygen radical species, leading to improvement in diastolic function as well as enhanced endothelial function [40].

There are limitations to who can receive the therapy due to availability of treatment, and hence clear guidelines are warranted to commission this treatment option to patients with worsening heart failure control despite optimal medical therapy.

The Role of Cardiac Rehabilitation Programmes

Cardiac rehabilitation programmes play a significant role in patients with HF. Guidelines from the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) recommend CR for HF patients to enhance physical activity and QOL, especially for those with severe disease and comorbidities [6,36,41–45]. A multidisciplinary specialist team is involved in the assessment and referral for rehabilitation. A typical cardiac rehabilitation programme includes medical evaluation, education on medication adherence, dietary advice, psychosocial support, and physical activity counselling [46,47]. CR should be provided in a convenient setting (at home, in the community or in the hospital).

NICE guidelines recommend exercise training (ET) as an adjunct to medical therapy in patients with HF based on the results of trials such as HF-ACTION [42,43,46]. HFrEF patients already established on optimal GDMT should also be considered for enrolment. In patients with HFpEF where the efficacy of GDMT remains uncertain, ET can also be considered [46]. Structured exercise training includes high intensity training (HIIT) or moderate continuous training (MCT) carried out for varying lengths of time. A personalised, exercise training programme should be considered during hospital admission and include an assessment appointment within 10 days of discharge from hospital. It should include clear and concise education and information surrounding exercise including the effects on psychological wellbeing [46].

Efficacy of exercise training in HFpEF

Mueller et al. found that exercise training in patients with HFpEF improved peak oxygen uptake (pVO2) by 8.0% ± 15.7%, whereas the control group experienced a reduction of 2.0% ± 18.3% (P=0.001) [48]. There was a strong correlation between increased exercise training, and elevated pVO2 at 4 months and at 1-year follow-up [44,49]. Supervised high-intensity interval training (HIIT) and moderate continuous training (MCT), have been analysed for their impact on pVO2 [13,45]. HIIT aimed to use 80-90% of heart rate reserve, the difference between a person's maximum heart rate and their resting heart rate, during four minute intervals separated by three minutes of recovery while MCT only used 35-50% of the heart rate reserve five times a week during 40 minute sessions [48]. MCT was found to be the most effective training modality, displaying an increase in pVO2 of 1.6 (2.5) ml/kg/min at 3 months, compared to 1.1 (3.0) ml/kg/min for HIIT and -0.6 (3.3) ml/kg/min for the control group (p=0.002) [48]. Contrarily, another randomised control trial highlighted the superiority of HIIT, which showed an increase in pVO2 of 3.5 (3.1-4.0) compared to 1.9 (1.2-2.5) for MCT at 3 months (p<0.001) [45]. This discrepancy underscores the necessity for determining the best training modality for individual patients. Despite this inconsistency, diastolic function achieved significant improvement regardless of what training method was used [45].

The effect of ET has also been evaluated using the 6MWTD. A multicomponent behavioural exercise intervention focussed on improving clinical outcomes in HFpEF demonstrated significant increases in walking distance compared to the enhanced usual care group (EUCG) at 6, 12, and 18 months [50]. The EUCG patients were provided with paid access to a fitness center to exercise independently without the behavioural support and exercise coaching provided. HFpEF patients undergoing ET also showed enhanced walking distances compared to the control group (p<0.001) [50] when required to perform at least 120 minutes of moderate-intensity exercise per week (using a heart rate monitor to ensure exercise intensity stayed within 40-80% of heart rate reserve) with significant results at 12 and 18 months of follow up [50]. Pandey et al. compared MCT in both HFpEF, and HFrEF patients revealed a significant increase in peak oxygen consumption in the HFpEF group (18.7±17.6%) compared to the HFrEF group (-0.3±15.4%) (P<0.001), although changes in 6MWTD were not statistically significant [51,52].

Data on the impact of ET on hospitalisation rates and mortality in HFpEF patients are limited. However, a pilot study of 50 patients reported fewer hospitalisations in the ET group [53]. Additionally, a cardiac rehabilitation programme involving 85 patients, showed lower hospitalisation and lower cardiovascular mortality in the exercise intervention group (11%) compared to the control group (24%) at 6 months follow-up. At 18 months, there was no significant difference between the intervention group (25%) and the control group (29%), however [54]. These studies' small sample sizes indicate the need for further large-scale research to determine the effect of ET. Table 1 summarises the trials on the efficacy of exercise training in HFpEF patients.

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Table 1. [HFpEF trials table]. Efficacy of exercise training in HFpEF.

	Scaling Peak Oxygen Consumption for Body Size and Composition in People With a Fontan Circulation (13)	One-Year Committed Exercise Training Reverses Abnormal Left Ventricular Myocardial Stiffness in Patients With Stage B Heart Failure With Preserved Ejection Fraction (44)	High-intensity interval training is effective and superior to moderate continuous training in patients with heart failure with preserved ejection fraction: A randomized clinical trial (45)	Effect of High-Intensity Interval Training, Moderate Continuous Training, or Guideline-Based Physical Activity Advice on Peak Oxygen Consumption in Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial (48)
Study type	Secondary data analysis	RCT	RCT	RCT
Method	Ratio and allometric (log-linear regression) scaling of VO_{2peak} to BM, stature, body surface area and fat free mass (n=89)	High-intensity exercise training HIIT (n=30) or attention control (n=16)	HIIT (n=10) vs MCT (n=9)	Exercise training ET (n=106) vs guideline control CON (n=52)
Results	Significant correlation between ratio scaled VO_{2peak} and BM (r=-0.25, p=0.02), stature (r=0.46, p<0.001) and body surface area (r=0.23, p=0.03), and not with fat free mass (r≤0.11; R^2=1%) No significant correlation between allometrically expressed VO_{2peak} and any scaling denominator were not (r≤0.11; R^2=1%)	Significant increase in VO_2 max with HIIT (from 26.0 ±5.3 to 31.3±5.8 mL/min/kg, P<0.0001) and LVEDV (p<0.0001) No significant change in VO_2 max (from 24.6±3.4 to 24.1±4.1 mL/min/kg, P=0.986) or LVEDV (p=0.175) in controls Unchanged resting blood pressure in both groups. LV myocardial stiffness was reduced with HIIT (LV chamber stiffness: from 0.060±0.031 to 0.042±0.025; LV myocardial stiffness: from 0.062±0.020 to 0.031±0.009) No significant change in controls (LV chamber stiffness: from 0.041±0.016 to 0.049±0.020; LV myocardial stiffness: from 0.061±0.033 to 0.066±0.031)	Significant increase in VO_{2peak} in both groups (HIIT 22.7%, MCT 11.3%; p<0.001) Peak oxygen pulse, estimate of stroke volume, increased more favourably in HIIT group First ventilatory threshold (anaerobic threshold) increased similarly in both groups (12.1 ± 0.6 to 13.4 ± 0.7 and 11.5 ± 0.8 to 12.6 ± 0.8 $mL \cdot kg^{-1} \cdot min^{-1}$, for MCT and HIIT, respectively, $p < 0.001$ for time comparison) No difference in peak RER between groups	Relative peak VO_2 increased by 8.0 ± 15.7% in the ET group compared with a reduction of −2.0 ± 18.3% in the CON group. The difference in change between groups was primarily mediated by changes in peak O_2-pulse (~72%) Mean changes were significantly different between ET and CON for relative peak VO_2, absolute peak VO_2, peak O_2-pulse and weight ($P < 0.05$) No significant differences have been observed for the change in peak HR, haemoglobin or peak respiratory exchange ratio (RER)

Efficacy of exercise training in HFrEF

The efficacy of exercise training has been evaluated more widely in HFrEF patients. Similar to HFpEF patients, ET has been shown to improve peak oxygen consumption in patients with HFrEF. In the HF-ACTION trial, which included 2331 HFrEF patients assigned to either an ET group or a usual care group (UCG), the ET group exhibited significantly better improvements in pVO2 at both 3 months, and 12 months compared to the UCG [55]. The ET group had a significant improvement in 6MWTD at 3 months, but this difference was not significant at 12 months [55]. The decline in 6-minute walk test distance at 12 months may result from decreased adherence to exercise, disease progression. worsening comorbid conditions, medication side effects, or lifestyle changes. The need for ongoing adjustments to the exercise program may also play a role in the reduced benefits observed over time.

Different exercise modalities have also been examined for their impact on pVO2. A 3-week interval training programme demonstrated a 21% increase in pVO2 in the high-intensity interval training (HIIT) group (n=16) compared to a 5% increase in the moderate continuous training (MCT) group (n=15) (P=0.009) [56]. Additionally, a multicentre trial with 215 patients randomly assigned to HIIT, MCT, or regular exercise (RRE) for 12 weeks found significant improvements in pVO2 for both HIIT (1.4; 0.2-1.6, P=0.02) and MCT (1.8; 0.5 to 3.0, P=0.003) compared to the RRE group, though no significant difference was noted between HIIT and MCT (-0.4; -1.7 to 0.8, P=0.70) [57].

The Aristos-HF trial, which included 88 HFrEF patients, demonstrated improved pVO2 across various exercise modalities, including aerobic training (AT- MCT and HIIT), AT and resistance training (RT), AT and inspiratory muscle training (IMT); and ARIS (a combination of AT+RT+IMT) for 180 minutes/week for 12 weeks with the greatest increase seen in the ARIS group [58]. The Aristos-HF trial also found the greatest improvement in 6MWTD in the ARIS group (55.2 [27.6 to 82.7], P≤0.001) [58]. A 4-month non-randomised study of combined resistance and endurance training involving 27 HFrEF patients showed a significant increase in pVO2, compared to an untrained group (n=22). [59].

ET has also been shown to improve left ventricular ejection fraction and reduce left ventricular end-diastolic dimension (LVEDD) in HFrEF patients. In a 3-week interval training programme, there was an increase in LVEF in the HIIT group (3.3%, P=0.034), though intergroup changes between HIIT, and MCT were non-significant compared to each other. [56]. Another trial evaluating LVEDD displayed a significant difference in LVEDD reduction in the HIIT group compared to the regular exercise group (-2.8 mm; -5.2 to -0.4 mm; P=0.02), but not between HIIT and MCT (-1.2 mm; -3.6 to 1.2 mm; P=0.45) [57]. NT-proBNP levels, another parameter analysed in HFrEF patients, showed no significant difference between the HIIT, MCT and RRE regimens [57]. The Aristos-HF trial found the greatest improvement in left ventricular end-systolic diameter (LVESD) in the ARIS group, with all interventions improving left ventricular end-diastolic dimension (LVEDD) and LVEF [58].

Mortality and hospitalisation rates following ET in HFrEF patients have been insufficiently reported. The HF-ACTION trial found no significant difference in mortality rates between the ET group (16%) and UCG (17%) at a median follow-up of 30 months (P=0.70), and all-cause hospitalisation rates were also similar (P=0.79) [55]. Conversely, a home-based cardiac rehabilitation (CR) randomized control trial reported lower hospitalisation rates in the CR group (5%) compared to the control group (14%), reducing readmission rates by nearly 10% over 12 weeks [60]. Further studies are necessary to determine the effect of ET on hospitalisation and mortality rates.

Patients with an elevated level of NT-proBNP exhibit higher risks of cardiovascular disease and mortality regardless of previous cardiovascular history and combined training showed a significant reduction in NT-proBNP levels. [59,61–65]. Finally higher levels of physical activity have been associated with a decrease in cardiovascular disease events. In a multivariable model, increased physical activity was linked to a reduced incidence of CVD events (HR: 0.802; 95% CI: 0.719-0.896; P<0.001) [64]. Routine physical activity has further shown a reduction in biomarkers of systemic inflammation which is present in progressive HF. [65] Figure 2 presents the impact of ET on HF patients while Figure 3 looks at the effect ET exhibits on VO2 and the 6MWT. The summaries of the trials on the efficacy of exercise training in HFrEF patients can be seen in Table 2.

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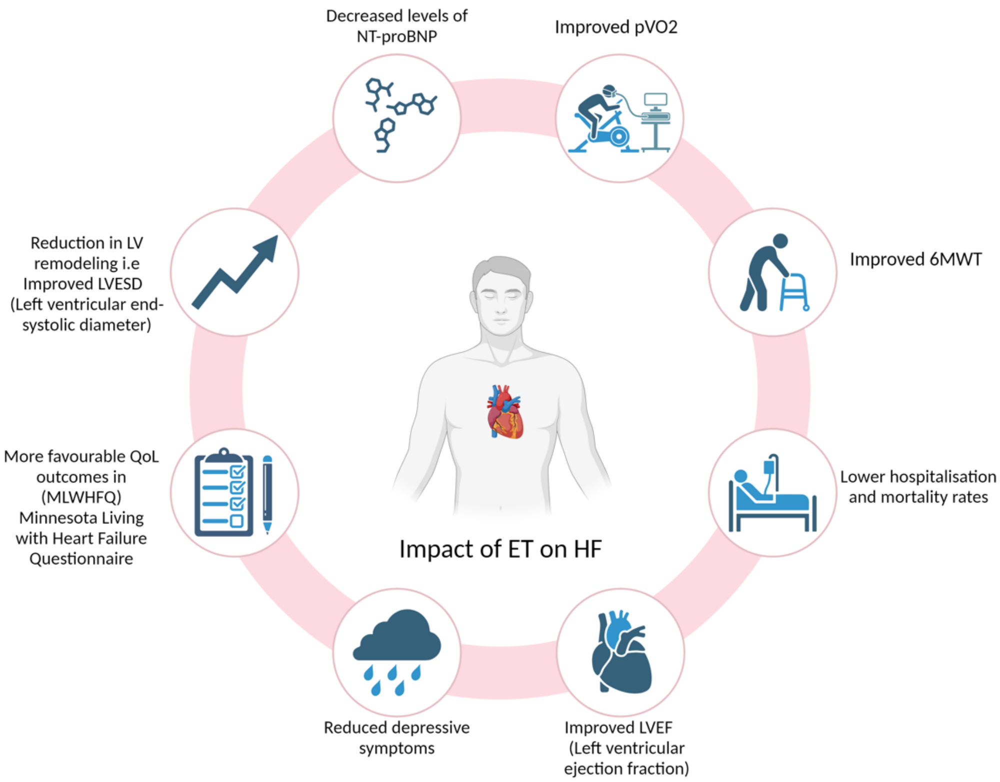

Figure 2. [Impact of ET on HF].

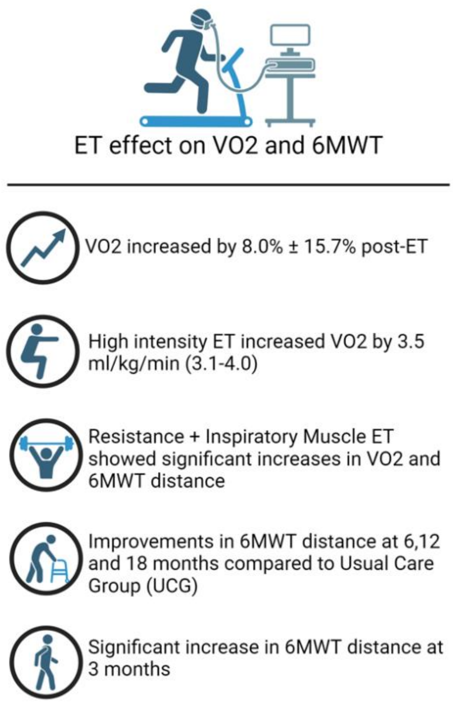

Figure 3. [ET effect on VO2 and 6MWT].

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Table 2. [HFrEF trials table]. Efficacy of exercise training in HFrEF.

	Response to Endurance Exercise Training in Older Adults with Heart Failure with Preserved or Reduced Ejection Fraction (51)	Efficacy and Safety of Exercise Training in Patients With Chronic Heart FailureHF-ACTION Randomized Controlled Trial (55)	Short-term effects of a 3-week interval training program on Heart Rate Variability in chronic heart failure. A randomised controlled trialShort-term effects of a 3-week interval training program on Heart Rate Variability in chronic heart failure. A randomised controlled trial (56)	High-Intensity Interval Training in Patients With Heart Failure With Reduced Ejection Fraction (57)	Combined aerobic/resistance/inspiratory muscle training as the 'optimum' exercise programme for patients with chronic heart failure: Aristos-HF randomized clinical trial (58)
Study type	Secondary analysis of an RCT	RCT	RCT	RCT	RCT
Method arms	Individuals with HF (24 HFrEF, 24 HFpEF) who underwent supervised exercise training.	Usual care plus aerobic exercise training (n=1159) vs usual care alone (1172)	MICT (*n* = 15) vs HIIT (*n* = 16)	HIIT, (n=77), MCT (n=65), vs recommendation of regular exercise (RRE) (n=73).	ARIS (19) vs AT/IMT (n=20) vs AT/RT (n=17) vs AT (n=18)
Results	Both groups combined, endurance training had 9.2% increase in VO_{2peak} (ml/kg/min) with substantial individual-level variability in the change in response to training. Improvement in VO_{2peak} in response to training was considerably higher in HFpEF vs. HFrEF patients (18.7±17.6 vs. −0.3±15.4%; p<0.001). Similar pattern was observed with absolute VO_{2peak} (ml/min)	759 (65%) patients in the exercise group died or were hospitalised, compared with 796 (68%) in the usual care group (hazard ratio [HR], 0.93; 95% confidence interval [CI], 0.84–1.02; *P* = .13) Nonsignificant reductions in the exercise training group for mortality (189 [16%] in the exercise group vs 198 [17%] in the usual care group; HR, 0.96; 95% CI, 0.79–1.17; *P* =	High-frequency power in normalised units (HFnu%) measured as HRV increased with HIIT (from 21.2% to 26.4%, *P* < 0.001) but remained unchanged with MICT (from 23.1% to 21.9%, *P* = 0.444, with a significant intergroup difference, *P* = 0.003) Resting heart rate decreased significantly for both groups (from 68.2 to 64.6 bpm and 66.0 to 63.5 bpm for MICT and HIIT, respectively, with no intergroup difference, *P* = 0.578) No difference in premature ventricular contractions	Change in LVED diameter from baseline to 12 weeks was not different between HIIT and MCT (*P*=0.45); LVED diameter changes compared with RRE were −2.8 mm (−5.2 to −0.4 mm; *P*=0.02) in HIIT and −1.2 mm (−3.6 to 1.2 mm; *P*=0.34) in MCT No difference between HIIT and MCT in peak oxygen uptake (*P*=0.70), but both were superior to RRE.	Between-group analysis showed a trend for increased $peakVO_2$(mL/kg/min) [mean contrasts (95% CI)] in the ARIS group [ARIS vs. AT/RT 1.71 (0.163–3.25), vs. AT/IMT 1.50 (0.0152–2.99), vs. AT 1.38 (−0.142 to 2.9)] Increased LVES diameter (mm) [ARIS vs. AT/RT −2.11 (−3.65 to (−0.561)), vs. AT −2.47 (−4.01 to (−0.929))] 6MWT (m) [ARIS vs. AT/IMT 45.6 (18.3–72.9)**, vs. AT 55.2 (27.6–82.7)]

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	Training-related increases in other measures of exercise capacity, including exercise time and ventilatory anaerobic threshold, were also greater in HFpEF vs. HFrEF patients, with trends towards statistical significance. No significant difference in change in 6MWT between the two groups	.70), cardiovascular mortality or cardiovascular hospitalisation (632 [55%] in the exercise group vs 677 [58%] in the usual care group; HR, 0.92; 95% CI, 0.83–1.03; *P* = .14), and cardiovascular mortality or heart failure hospitalisation (344 [30%] in the exercise group vs 393 [34%] in the usual care group; HR, 0.87; 95% CI, 0.75–1.00; *P* = .06) Other adverse events were similar between the groups.	Improvement in peak oxygen uptake was greater with HIIT than MICT (+ 21% vs. + 5%, *P* = 0.009) LVEF improved with only HIIT (from 36.2% to 39.5%, *P* = 0.034).	However, none of these changes was maintained at follow-up after 52 weeks. Serious adverse events were not statistically different during supervised intervention or at follow-up at 52 weeks (HIIT, 39%; MCT, 25%; RRE, 34%; *P*=0.16).

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Resistance exercise training modality

Changes in muscle function and composition are important determinants in the prognosis of HF patients. The effectiveness of resistance exercise training (RET) has been evaluated in patients with sarcopenia. It usually involves muscle contraction against external resistance with the aim of increasing muscle strength, tone or mass. One trial focused on a 12- week resistance training programme in 10 stable HF patients and demonstrated a marked increase in quadriceps strength ($p<0.01$) but not muscle mass ($p>0.2$) [52]. A randomised control trial of RET and nutritional supplementation on muscle size and strength in 94 generally frail patients (not specifically HF patients [66]) showed that muscle strength and size of hip and knee extensors improved significantly ($P=0.001$), improving mobility and physical activity levels [66]. RET may help frail HF patients adjust and take part in aerobic training, however further studies are required.

Ventilatory assistance

Ventilatory assistance, the use of mechanical pressure support to aid breathing, has been shown to reduce ventricular preload and afterload and to improve the work of breathing in decompensated HF patients. This involves improving oxygenation of myocardial tissue and optimising cardiac output requirements [67]. A randomised controlled trial including stable chronic HF patients studied the effect of ventilatory assistance) on exercise endurance [68]. Exercise time improved significantly with pressure support in comparison to the control group ($P=0.004$). In contrast, CPAP only produced a small improvement on exercise time ($p=0.079$) [68]. The positive effects of ventilatory assistance could be applied in patients unable to adhere to ET, however further research is necessary to ascertain the viability of this option.

Exercise Training and Quality of Life in Heart Failure

Quality of life for HF patients is assessed using the Minnesota Living with Heart Failure Questionnaire (MLWHFQ), the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Short Form Health Survey (SF-36), among others [36,69]. The MLWHFQ consists of 21 questions scaled 0-5 to indicate the effect of heart failure during the last 4 weeks. The final score is summation of all responses. This questionnaire reflects the impact of heart failure on patient lives in both the physical, emotional and socioeconomic domains [70]. The KCCQ contains 23 items, covering 6 domains – symptom, physical function, QoL, social limitation, self-efficacy and symptom stability; and 2 summary scores – clinical summary and overall summary for a total scale of 0-100 [71]. As the name suggests, the SF-36 consist of 36 questions, with 8 weighted domains – vitality, physical function, bodily pain, general health perception, physical role, emotional role, social role and mental health, for a total score between 0 and 100 [72]. These quesionnaires have been used when assessing patients' responses to exercise ET.

Studies assessing QOL following ET in HFpEF

A study involving 116 HFpEF patients used the MLWHFQ and the SF-36 questionnaires. Post-intervention, MLWHFQ scores were lower in the ET group (23.13, 95% CI, 18.32-27.95) compared to the control group (CG) (28.20, 95% CI, 23.61-32.79). SF-36 showed better outcomes for the ET group in the domains of role-physical ($P<0.05$), vitality ($P<0.05$), and role-emotional compared to the CG. Interestingly, no significant association was found between pVO2 or 6MWTD and HRQoL changes in the ET group, however [49]. This may be due to the patient-centered nature of HRQoL assessments, which capture emotional and psychological benefits not always reflected in physical measurements. Individual responses, assessment timing, and the complex interplay of physical and non-physical factors may contribute to this disconnect. Thus, improvements in QoL can occur independently of changes in physical fitness.

Two studies using the KCCQ questionnaire [48,50]. One found no significant change in QoL after 3 months between high-intensity interval training (HIT), moderate continuous training (MCT),

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and CG. However, after 12 months, the MCT group reported significantly higher QoL outcomes compared to the CG (11, 95% CI, 2-19). No significant difference was observed between the HIT group and the CG after 12 months (4, 95% CI, -3 to 12) [48]. Another study indicated that KCCQ scores improved significantly in the home-based care ET group (HCG) after 18 months, compared to the usual care group [50].

Studies have assessed the effect of ET on depression in HFpEF. Analysis of the HEART camp group trial demonstrated a statistical improvement in depression post intervention ($p=0.029$) [71]. Another study utilising the hospital anxiety and depression score (HADS) displayed a mild decrease in depression at 6 months (8, 7-9) in comparison to baseline (7.5, 6-8) [54].

Studies assessing QOL following ET in HFrEF

The Aristos-HF trial demonstrated significant benefits in MLWHFQ scores for the aerobic resistance interval training (ARIS) and aerobic training/inspiratory muscle training (AT/IMT) groups ($P \leq 0.0001$) [58]. Additionally, a randomized controlled trial involving 33 HFrEF patients who underwent high-intensity interval training (HIIT) and 39 patients who did not participate in exercise training found significant improvements in health-related QoL outcomes in the intervention group. MLWHFQ scores significantly decreased (indicating improved QoL) in the intervention group after 12 weeks, while no change was observed in the control group (intergroup changes, $P<0.001$) [73,74].

A multicentre trial reported no significant differences in QoL outcomes between ET and control groups using the KCCQ [57]. Another multicentre trial demonstrated no difference in hospital and anxiety scale in HFrEF post intervention [57], while a study utilising the Zung depression rating scale (ZDRS) found a significant improvement in the ET intervention group ($p=0.005$), while it was similar in the control group compared to the intervention group ($p=0.19$)[74]. Studies that have analysed the effect of ET on depression do not appear to show significant improvement in HFrEF patients. An overview of ET effect on QoL can be seen on Figure 4.

The benefits observed in specific QoL measures suggest that personalised treatment approaches and longer-term follow-up are essential with more RCTs required to confirm the present findings.

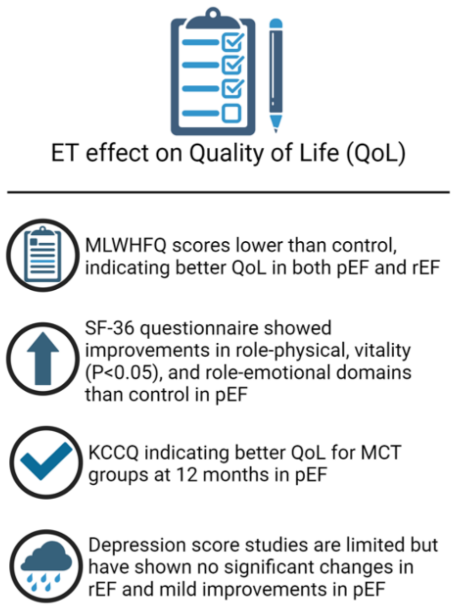

Figure 4. [ET effect on QoL].

Adherence to Exercise Training

Maintaining adherence to ET can be challenging and is generally higher in supervised programs, and when personalised strategies are implemented. Current NICE guidelines state that a personalised, exercise-based cardiac rehabilitation programme should be offered unless the patients' condition is unstable [46]. This should include a psychological and educational component, and be provided in a format and setting that is easily accessible for the patient [46]. While specific training exercises are not mentioned consistent adherence and attendance are required to see clinical benefit [75] .

HFpEF

A study comparing high-intensity interval training (HIT) and moderate continuous training (MCT) in HFpEF patients found high adherence rates at 3 months. Specifically, 80.4% of participants in the HIT group and 76.4% in the MCT group adhered to at least 70% of the exercise sessions. The median weekly exercise duration was 96 minutes (IQR, 82-105) for HIT and 176 minutes (IQR, 137-188) for MCT. However, adherence decreased during the home phase (4-12 months) to 77 minutes per week (IQR, 46-92) for HIT and 144 minutes per week (IQR, 108-171) for MCT [48]. The HEART camp trial highlighted better long-term adherence in the home-based care group (HCG) compared to the usual care group (UCG). At 12 months, 42% of HCG participants adhered to the exercise regimen, which increased to 56% at 18 months. Conversely, adherence in the UCG dropped from 14% at 12 months to 0% at 18 months [50]. Another study found that 48 out of 58 HFpEF patients in the exercise training group (ETG) completed the final testing, achieving an adherence rate of 88% for the prescribed physical activities [49]. Fiatarone et al had a mean adherence rate of 97 percent for RET in frail patients [76].

HFrEF

A multicentre trial for HFrEF patients reported perfect adherence rates in both HIT and MCT groups, with participants completing 100% of their sessions (35 of 35 for HIT and 4 of 4 for MCT) [57]. Additionally, a 16-week supervised ET program showed a high adherence rate of 93.75%, with patients completing 45 of 48 sessions [76].

A sub-study investigating predictors of adherence to ET programs in HFrEF patients identified that a new diagnosis of heart failure significantly predicted adherence (p=0.03) [77]. Meeting the exercise guideline (150 minutes per week of moderate exercise) at follow-up was more likely in those with a new diagnosis of heart failure (p=0.0013) and those who were physically active at baseline (p=0.007). The study concluded that individualised approaches are necessary to enhance adherence, particularly for decompensated heart failure patients and those who are initially inactive [76,77].

Further research is essential to develop effective supervision methods and improve long-term adherence rates of ET in both HFpEF and HFrEF patients.

Prescription rates

There are generally poor prescription rates for ET in HF patients. Frail HF patients are unable to take part in vigorous exercise training which may illicit a contributing factor to poor prescription and adherence rates. Patient motivation, socio-cultural factors and burden of travel to cardiac rehabilitation centres are additional key factors affecting prescription rates. In a study of 513 patients with HFpEF and HFrEF, 100 percent were educated on the benefits of exercise; however, only 21 (4%) were enrolled in a supervised exercise programme [77]. A survey of 170 European cardiac centres found that 67 (39.4%) did not provide an ET programme [78]. This was mainly ascribed to a lack of resources and staff. In the US, out of 397000 HFrEF Medicare patients eligible for an ET regimen, only 2.6% completed more than one training session in a 12-month timeframe [79]. Furthermore, of those prescribed cardiac rehabilitation, only 20% completed all the sessions.

Conclusions and Recommendations

Combining GDMT with exercise-based therapy has additional benefits for HF patients, improving functional capacity, exercise tolerance and HRQOL outcomes. Prescription rates are low across different healthcare systems and there are currently no well-established guidelines on establishing personalised regimens. Clinical characteristics (comorbidities, frailty status, exercise capacity, personal needs) of patients are necessary when selecting patients for ET. A tailored approach of ET methods matched to a patient's baseline characteristics appears to be most effective. An MDT with involvement of occupational and physiotherapy should play a role in the assessment for ET. Involvement of primary care in the longer-term management of ET should be explored. This includes arranging follow ups for the patients' clinical status with questionnaires assessing QoL and adherence rates. Initial assessment should include selection of an age-appropriate programme with ventilatory assistance offered to the advanced HF population.

ET is a medicine and incorporating it as part of the overall management strategy is necessary.

Limitations

Heterogeneity in study population, study design and exercise-based cardiac rehabilitation-intervention was evident making meta-analysis challenging. In addition, the trials reported have not adequately assessed the long-term effects of exercise training in the HF population. Insufficient data is reported on the hospitalisation and mortality rates following ET. Some studies reviewed did not include whether patients were established on GDMT. A limited number of studies reported QoL outcomes after ET. Further work is vital to address these limitations to aid efficacious exercise prescriptions for HF patients.

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