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# Clinical Utility of Exercise Training in Heart Failure with Reduced and Preserved Ejection Fraction

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**ABSTRACT:** Reduced exercise tolerance is an independent predictor of hospital readmission and mortality in patients with heart failure (HF). Exercise training for HF patients is well established as an adjunct therapy, and there is sufficient evidence to support the favorable role of exercise training programs for HF patients over and above the optimal medical therapy. Some of the documented benefits include improved functional capacity, quality of life (QoL), fatigue, and dyspnea. Major trials to assess exercise training in HF have, however, focused on heart failure with reduced ejection fraction (HFREF). At least half of the patients presenting with HF have heart failure with preserved ejection fraction (HFPEF) and experience similar symptoms of exercise intolerance, dyspnea, and early fatigue, and similar mortality risk and rehospitalization rates. The role of exercise training in the management of HFPEF remains less clear. This article provides a brief overview of pathophysiology of reduced exercise tolerance in HFREF and heart failure with preserved ejection fraction (HFPEF), and summarizes the evidence and mechanisms by which exercise training can improve symptoms and HF. Clinical and practical aspects of exercise training prescription are also discussed.

**KEYWORDS:** heart failure, exercise, HFPEF

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## Introduction

Heart failure (HF) is a chronic and debilitating illness that is becoming an increasingly important burden on the health care system. The American Heart Association (AHA) reported the prevalence of HF in American population as 2.6% in 2006, with more than 200,000 deaths associated with HF.[1] There is good evidence that the burden of HF syndrome is increasing in the developed countries mainly because of improved survival and aging population. Approximately 550,000 individuals in the United States are diagnosed with HF annually, and this number is anticipated to increase to 1.5 million by 2040. Recent large epidemiological studies have established that at least one-half of patients with HF indeed have preserved ejection fraction (EF), termed as heart failure with preserved ejection fraction (HFPEF), and that this portion of the HF population predominantly consists of women, older age group, and people with hypertension and other cardiovascular risk factors.[2] The prevalence of HFPEF within the population varies from 1.14% to 5.5%, depending on the age of the population.[2] To establish a diagnosis of HF, the contemporary guidelines warrant the presence of symptoms and signs specific to HF, and objective evidence of cardiac dysfunction, usually by echocardiography. Similarly, three obligatory conditions need to be satisfied to diagnose HFPEF are clinical signs and symptoms of HF, normal or near normal systolic function, and diastolic dysfunction.[3,4]

Exercise training for HF patients is well established as an adjunct therapy. Until only three decades ago, bed rest and the restriction of exercise were recommended for people with HF. This concept, however, was challenged in 1980s. The first study on the effects of exercise in HF was published in 1990,[5] which reported improvement of HF symptoms and physical capacity with exercise training, without adverse events. The authors concluded that the belief that bed rest was beneficial in preserving the hearts of HF patients could no longer be accepted. This was followed by further studies that suggest that reduced exercise tolerance is in fact an independent predictor of hospital readmission and mortality in patients with HF.[6,7] Today, an exercise program is formally recommended as an important and safe treatment for HF patients.[8–10]

The aims of this review are (1) to discuss the clinical and practical aspects of exercise training prescription, (2) provide a brief account of pathophysiology of reduced exercise tolerance in HF, and (3) summarize the evidence and mechanisms by which exercise training can improve symptoms of HF in people with heart failure with reduced ejection fraction (HFREF) and heart failure with preserved ejection fraction (HFPEF). Databases including Ovid EMBASE, Ovid MEDLINE, and PubMed were searched for terms (heart failure, diastolic heart failure, heart failure with normal ejection fraction, heart failure with preserved ejection fraction, exercise training, cardiac rehabilitation) up to December 2014.

## Exercise Prescription in HF Patients

Most contemporary guidelines generally suggest an aerobic activity of at least 30 minutes for five or more days per week. There is a great variation between the exercise programs and the level of intensity in HF trials. Clinically, an intensity range of 70–80% of peak heart rate (HR) is usually deemed as sufficient when a symptom-limited exercise protocol is utilized. The rating of perceived exertion (RPE) has also been used as an indicator for work intensity and as a tool in the prescription of exercise training intensity.[11] The RPE score has been shown to be reliable and valid, and it has a moderate to high correlation ($r$ range, 0.57–0.89) with respiratory variables, HR, and blood lactate in healthy men.[12] In HF, patients' RPE should be considered as an adjunct to a training intensity determined by the percentage of VO2peak (peak oxygen consumption; as a measure of exercise capacity), HR, blood pressure, and symptom monitoring because the RPE determined during graded cardiopulmonary exercise testing may not consistently translate to the same intensity as that during exercise training, and a certain percentage of patients are unable to reliably use the RPE scale. Since during exercise, ratings of fatigue and dyspnea are often differently perceived, both symptoms should be monitored separately.[10,12]

Although there is no consensus as to which methods and exercise intensities are better for the treatment of HF patients, the sub-maximum seems to offer a better safety/efficiency balance.[13] The most recent Australian guidelines recommend moderate-intensity training at 40–70% VO2peak with a graded increment in duration of exercise, initially from 10 to 15 minutes and increasing to 45–60 minutes per session.[14]

Studies have also looked into added utility of higher intensity exercise when compared to low–moderate-intensity levels, and have been postulated to have further beneficial effects on VO2peak, left ventricular (LV) remodeling, endothelial function, as well as mitochondrial function. Patwala et al.[15] have shown significant added improvement in VO2peak after a high-intensity training program that comprised 80–90% of peak HR. This additional benefit was more than that obtained after cardiac resynchronization therapy (CRT).

Although aerobic training (AT) remains the frontline of recommendations, resistance training has been associated with increased muscle power, endurance, and peripheral blood flow.[16,17] Levinger et al.[18] examined the effects of resistance training vs. usual activity in patients with HF and found modest improvements in resting EF despite unchanged LV volumes. A similar study examined the effect of resistance training on the capacity to perform activities of daily living (ADLs) and quality of life (QoL) in individuals with high number of metabolic risk factors (HiMF) compared with individuals with a low number of metabolic risk factors (LoMF).[19] Resistance training improved muscle strength and the capacity to perform ADLs in individuals with HiMF and LoMF. Resistance training improved QoL for the HiMF group, and this result was independent of changes in body fat content or aerobic power. A recent systemic review to evaluate resistance training, either alone or as an adjunct to AT, for improving cardiac function, exercise capacity, and QoL in people with HF[20] concluded that resistance training increased six-minute walk distance compared to no training, but had no other benefits on cardiac function, exercise capacity, or QoL if used alone or as an adjunct to AT in people with chronic HF.

Similarly, another recent study compared the combined aerobic and resistance training (ART) with an AT in a population of obese type 2 diabetic patients and metabolic syndrome. A total of 47 patients were randomly assigned to aerobic (27 patients) or aerobic plus resistance (20 patients) exercise trainings. Although this study did not particularly focus HF patients, it did show the difference in effects on the related outcomes. Both exercise programs equally improved body weight. Mean blood pressure (AT: –3.6 mmHg vs. ART: +0.6 mmHg, $P < 0.05$) and endothelin-1 (ET-1) incremental areas during walking test (AT: –11% vs. ART: +30%, $P < 0.0001$) decreased after AT and increased after ART. Adiponectin levels increased by 54% after AT, while decreased by 13% after ART ($P < 0.0001$) and matrix metalloproteinase-2 (MMP-2), tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) levels significantly decreased in AT, while increased in the ART group. This study suggested that ART, as compared with AT, similarly enhanced body weight loss but exerted less positive effects on insulin sensitivity and endothelial factors, adipokines, and proinflammatory marker release.[21] Beckers et al also reported

that when comparing with RT alone, six months of ART resulted in a greater improvement of submaximal exercise capacity, upper extremity muscle strength, and cardiac symptoms.[16]

Despite the HF being a condition affecting primarily the elderly population, most of the studies have excluded patients with an age >70 years. Wisloff et al.[22] studied 27 patients with stable post-infarction HF with a mean age of 75.5 ± 11.1 years who were randomized to either moderate continuous training (MCT) (70% of peak HR) or aerobic interval training (AIT) (95% of peak HR) three times per week for 12 weeks or to a control group. The major finding of this study was that AIT was superior to MCT in patients with post-infarction HF with regard to LV remodeling reversal, aerobic capacity, endothelial function, and QoL. It demonstrated that high-intensity training relative to the individual's maximal oxygen uptake is feasible even in elderly patients.

In summary, although there is no expert consensus on the mode of exercise, combined resistance and AT is likely to optimize the benefits by acting on both the central and peripheral pathways. It is superior to aerobic exercise alone for improving QoL, endurance, and muscle strength.[16] A training approach to combined ART can minimize hemodynamic burden by focusing on small muscle groups and maximizing peripheral adaptations.[14] The benefits of resistance training in isolation are not clear. Any recommendation for exercise training in HF should be based on the particular pathology of the patient, the individual's response to exercise (including HR, blood pressure, symptoms, and perceived exertion), and measurements obtained during cardiopulmonary exercise testing. Additionally, patient's individual status, including current medication, risk factor profile, behavioral characteristics, personal goals, and exercise preferences, should be taken into consideration.[10] Absolute and relative contraindications for exercise training in HF patients are outlined in Table 1.

## Pathophysiology of Exercise Intolerance in HF

Mechanisms involving the cellular metabolism and intracellular energy transfer in cardiac as well as skeletal muscle, sympathetic neural activation, and inflammatory cytokines, all possibly contribute to the development of exercise intolerance in HF (Table 2). Although central factors, such as EF or cardiac output, do play a role, it is mostly peripheral factors that are responsible for the reduction in exercise capacity.[23]

**Central pathophysiology and exercise intolerance.**

*Cardiac causes.*

1. LV dysfunction is characterized by a decrease in EF from the normal range of 60–70% to less than 45%.[8] This is followed by a reduction in stroke volume (SV)[24] and cardiac output, first during exercise and then subsequently at rest.[25,26] Although abnormalities in the central hemodynamic response have been described in patients with HF, there remains the paradox that measures of resting ventricular function, such as EF, demonstrate a poor correlation with exercise capacity.[27–29] However, an improvement in exercise capacity after CRT may be in part because of the improvement in systolic function.[15] The response to exercise in the patient with systolic HF is characterized by inadequate LV shortening with increases in end-systolic and end-diastolic volumes. Diastolic dysfunction, on the other hand, is characterized by impaired LV distensibility during exercise, resulting in a rapid rise in LV diastolic pressure and pulmonary capillary wedge pressure that result in symptoms of dyspnea.[29]
2. Reduced cardiac output because of a low SV as well as a lower HR reserve.[30]
3. Elevated LV pressure can lead to pulmonary congestion, particularly on exercise, which may result in secondary pulmonary hypertension with time. This in turn may affect the right ventricular function.[4]

**Table 1.** Contraindications for exercise training in HF[14].

| ABSOLUTE CONTRAINDICATIONS | RELATIVE CONTRAINDICATIONS |
|---|---|
| Progressive worsening of exercise tolerance or dyspnea at rest or on exertion over previous 3–5 days | ≥2 kg increase in body mass over previous 1–3 days |
| Significant ischemia at low exercise intensities (<2 METS, or <50 W) | Concurrent continuous or intermittent dobutamine therapy |
| Uncontrolled diabetes | Decrease in systolic blood pressure with exercise |
| Acute systemic illness or fever | New York Heart Association Functional Class IV |
| Recent embolism | Complex ventricular arrhythmia at rest or appearing with exertion |
| Thrombophlebitis | Supine resting heart rate ≥100 bpm |
| Active pericarditis or myocarditis | Pre-existing comorbidities |
| Severe aortic stenosis | Moderate aortic stenosis |
| Regurgitant valvular heart disease requiring surgery | BP >180/110 mmHg (evaluated on a case by case basis) |
| Myocardial infarction within previous 3 weeks | |
| New onset atrial fibrillation | |
| Resting heart rate >120 bpm | |

**Table 2.** Pathophysiological causes of exercise intolerance in HF and improvement in these pathologies that is associated with exercise.

| PATHOPHYSIOLOGY | IMPROVEMENT ASSOCIATED WITH EXERCISE |
|---|---|
| Central causes<br>• Left ventricular dysfunction leading to reduced stroke volume and cardiac output<br>• Reduce chronotropic reserve<br>• Pulmonary congestion secondary to LV dysfunction<br>• Functional mitral regurgitation<br>• Exaggerated minute ventilation relative to carbon dioxide production<br>• Pulmonary structural abnormalities<br>• Poor inspiratory muscle performance | • Improvement of cardiac output at peak exercise level<br>• Reduction of resting left ventricular end-diastolic diameter<br>• Reduced left ventricular diastolic wall stress<br>• 30% increase in VO2peak<br>• Improved functional capacity in people with dilated cardiomyopathy and diastolic dysfunction<br>• Inspiratory muscle training improves symptoms, VO2peak and cardiac performance |
| Peripheral causes<br>• Reduced skeletal mass<br>• Alteration in skeletal fiber from type 1 to type IIb<br>• Decrease skeletal oxidative metabolism and ATP production<br>• Endothelial dysfunction<br>• Dysregulated neurohumoral system<br>• Production of inflammatory cytokines | • Improved skeletal mitochondrial load and oxidative metabolism<br>• Reverse-shift from type IIb skeletal muscle fibers to type I<br>• Improved peripheral blood flow with more efficient energy delivery<br>• Improvement of endothelial dysfunction<br>• Reduced NADPH and ROS generation<br>• Reduced sympathetic activity<br>• Reduced production of TNF-$\alpha$ and IL-6 |

4. Functional mitral regurgitation (MR) can be a consequence of dilated cardiomyopathy or papillary muscle dysfunction leading to reduced SV.[31,32]
5. Reduced chronotropic reserve in HF, ie, an inability to increase the HR in response to exercise, will lead to failure to increase cardiac output and result in dyspnea during exercise.[33]

*Respiratory causes.*

1. Exaggerated minute ventilation relative to carbon dioxide ($CO_2$) production – irrespective of the presence of pulmonary congestion, exercise in HF patients will result in a marked rise in minute ventilation, out of proportion to the respiratory rate-dependent raised $CO_2$ production, contributing to potential significant pulmonary ventilation/perfusion mismatch.[34,35]
2. Structural abnormalities such as fibrosis and vascular injury, related to pulmonary hypertension and venous congestion, have been seen in HF.[35,36]
3. Alveolar edema secondary to pulmonary congestion.[35,36]
4. Poor inspiratory muscle performance is associated with dyspnea, poor exercise tolerance, and poor functional status in HF. Inspiratory muscle training has been observed to improve dyspnea, QoL, peripheral muscle and peripheral blood flow, HR, respiratory rate, VO2peak, and several indices of cardiac performance.[37]

**Peripheral pathophysiology and exercise intolerance.** While some studies claimed that poor exercise capacity in patients with HF is caused by a reduction in EF[38] and cardiac output,[39,40] most researchers have suggested that changes in the periphery are the main contributors to poor exercise capacity in these patients. These alterations include an increase in peripheral vascular resistance, changes in skeletal muscle metabolism, and reduction in skeletal muscle blood flow, mass, and strength.[41–48]

*Skeletal muscle causes.*

1. A reduced skeletal muscle mass has been seen in HF patients,[49] which in turn has been associated with reduced exercise capacity.[46]
2. An alteration in fiber type from type I to type IIb has been seen in HF patients. These type IIb fibers have fast vs. slow twitching and glycolytic vs. oxidative properties and affect aerobic exercise capacity adversely.[50]
3. Decreased oxidative metabolism and adenosine triphosphate (ATP) production – With maximal exercise testing, the HF patients typically report leg fatigue. This fatigue is associated with increased lactate release from the legs, evidence supportive of skeletal muscle dysfunction. Lactate levels correlate closely with maximal exercise capacity, suggesting a link between muscle dysfunction and exercise intolerance in HF. One study suggests that neither reduction in muscle oxidative capacity nor reduction in capillary density appears to be the cause of exercise limitation in patients with HF.[51] In this study, VO2peak was determined in 14 HF patients and 8 healthy sedentary similar-age controls. Muscle samples were analyzed for mitochondrial ATP production rate (MAPR), oxidative and glycolytic enzyme activity, fiber size and type, and capillary density. HF patients demonstrated a lower VO2peak ($15.1 \pm 1.1$ vs. $28.1 \pm 2.3$ mL·kg$^{-1}$·min$^{-1}$, $P < 0.001$) and capillary to fiber ratio ($1.09 \pm 0.05$ vs. $1.40 \pm 0.04$, $P < 0.001$) when compared with controls. However, there was no difference in capillary density (capillaries per square millimeter) across any of the fiber types. Measurements of MAPR and oxidative enzyme activity suggested no difference in muscle oxidative capacity between the groups. Based on these findings, the authors hypothesized that the low VO2peak observed in HF patients may be the result of fiber atrophy and possibly impaired activation of oxidative phosphorylation.

Studies have shown that patients who suffer from moderate–severe LV impairment have a reduced mitochondrial density and oxidative enzyme activity (citrate syntheses and β-hydroxyacyl CoA dehydrogenase).[52–56] Drexler et al.[57] found a decrease in both surface density and volume density of mitochondrial cristae (20% and 17%, respectively) in patients with severe CHF. These changes were consistent with a reduced oxidative capacity of skeletal muscle, from ~60% of mitochondria in normal subjects to ~17% of mitochondria in HF patients. As a result of reduction in oxidative enzyme activity, carbohydrate would be utilized as a source of energy instead of fat, which may result in early anaerobic metabolism and fatigue.[56] Kemp et al.[58] found that the non-oxidative ATP cost of work had increased by 150% during exercise in HF patients and was followed by glycogenolytic production, while there was a reduction in the oxidative cost by 26%. Furthermore, they reported a decrement in cytosolic pH with an increase in glycogenolysis during exercise when compared to the control group.

Both activity of oxidative enzymes and mitochondrial cristae surface density showed significant correlation with ventilator threshold and VO2peak in patients with HF (*r* between 0.56 and 0.82).[57,59–63] These findings suggest that a reduction in mitochondria number and/or its inability to utilize the oxygen delivered (secondary to a decrease in oxidative enzymes) may have contributed to the reduction in oxidative capacity, leading to an early onset of anaerobic metabolism and lactate production.[55,60,64,65]

*Other peripheral causes.* Endothelial dysfunction (associated with lower nitric oxide (NO) and impaired vasodilatory response to shear stress) and defects in neurohumoral system affecting sympathetic and parasympathetic activities, and proinflammatory cytokines, all have been associated with reduced exercise capacity in HF patients.[41–48]

Studies in the past decade have suggested that specific alterations in HFPEF consist of cardiomyocyte hypertrophy and interstitial fibrosis, whereas functional changes include incomplete relaxation of myocardial strips and increased cardiomyocyte stiffness. Furthermore, abnormal intramyocardial signaling evident from endothelial cells expressing adhesion molecules, inflammatory cells secreting profibrotic transforming growth factor β (TGF-β), and oxidative stress increasing nitrotyrosine content are also seen in this population.[66] In HFPEF, comorbidities contribute to a systemic inflammatory state, which induces oxidative stress in the coronary microvascular endothelium. This reduces myocardial NO bioavailability and leads to reduced protein kinase G activity in cardiomyocytes, which therefore become stiff and hypertrophied. This differs from myocardial remodeling in HFREF, which is driven by cardiomyocyte death because of oxidative stress originating in the cardiomyocytes as a result of ischemia, infection, or toxicity.[66]

**HFPEF and exercise intolerance.** It has been postulated that patients with HFPEF have concomitant arterial stiffening, contributing to increased LV afterload and alterations of systolic and diastolic functions, particularly during exercise.[67,68] The increased afterload consequently affects the diastolic filling, again particularly during exercise when a more efficient diastolic filling pressure is required,[29] and atrial function becomes a significant determinant of LV filling, thus leading to increased LV filling pressure.[69–71] Ultimately, it is the combined relationship between central and peripheral mechanisms, as detailed above, that forms the global ventricular–vascular interaction, and importantly, it is this relationship during exercise that contributes to HF symptoms.[72] Owing to the known beneficial effects on peripheral vascular resistance, arterial stiffening, and abnormalities of skeletal muscle metabolism in the HFPEF syndrome, exercise training presents a viable management and therapeutic tool.[72]

## Benefits of Exercise in HF

Many exercise benefits for HF patients have been documented, such as improvements in physical capacity (an increase in 10–30% of the maximum physical capacity),[73,74] QoL,[75] endothelial dysfunction,[76] circulating catecholamine levels,[77] morbidity, and hospital admissions.[78] These above-mentioned changes lead to increased overall exercise capacity with a lower required HR. Exercise training is now widely used as an adjunct therapy for the stable HF patients[79] with class 1 recommendation by the American College of Cardiology (ACC) and the AHA.[80]

Most HF trials have used moderate/high-intensity exercises (70–80% of peak HR). A lower intensity program of 40–50% VO2peak has also been shown to improve the exercise capacity.[75] The recent "Heart Failure – A Controlled Trial Investigating Outcomes of exercise TraiNing" (HF-ACTION) trial, a multicentre, randomized controlled trial looking at 2,331 HF patients with EF ≤35%, and New York Heart Association functional classes II–IV showed a nonsignificant reduction in the primary combined end-point of all-cause mortality or hospital stay (HR: 0.93; $P = 0.13$) after a moderate-intensity training followed by home-based training with a total of 30 months median follow-up. Furthermore, no difference in mortality was observed between the exercise and control arms (16% vs. 17%). Significant improvement in VO2peak was, however, noted in the exercise group (0.6 vs. 0.2 mL/kg/minute). It was, however, noted that only approximately 40% of the exercise group reported a training reaching the prescribed duration of 1.5 hours/week for the first three months, which would likely account for only modest increase in VO2peak, impacting on statistical differences in outcomes between the exercise and control arms.[81] As far as the adverse events related to exercise in HF patients are concerned, HF-ACTION showed no difference during the entire study period.[81]

**Role of exercise in HFPEF.** Major trials to assess exercise training in HF have focused on HFREF. Since the patients with HFPEF also experience exercise intolerance, dyspnea, early fatigue, and similar mortality risk and

rehospitalization rates, a case can be made for exercise to be part of the management of people with HFPEF.[79]

Gary et al.[82] have evaluated effects of exercise training on elderly women with HFPEF. A total of 32 women with New York Heart Association classes II and III HFPEF (LV EF >45% and symptoms of dyspnea or fatigue) were randomized into a 12-week home-based, low-to-moderate-intensity (40% and 60%, respectively) exercise and education program (intervention) or only education program (control). The intervention group improved in the six-minute walk test (+20% vs. –11%). Improved QoL and depression were also reported. Similar findings were demonstrated by Smart et al.[83] among 18 patients with HFPEF who improved their QoL and exercise capacity by 30%, although without a change in diastolic dysfunction. Kitzman et al.[84] randomized 53 patients with HFPEF to either a three days per week exercise program or control group. Increased exercise capacity and physical score (measured on Minnesota Living with Heart Failure Questionnaire) were seen after 16 weeks of training, while no change was observed in neuroendocrine or LV function.

Diabetes is common in HFPEF patients and is associated with increased ventricular stiffness. Subclinical diastolic dysfunction without HFPEF is a common complication of type 2 diabetes mellitus (T2DM) that is independently associated with poor cardiovascular outcomes.[85] To date, no study has demonstrated the ability to alter the progression of diastolic dysfunction in diabetes. Hare et al have studied the impact of an exercise-lifestyle intervention on diastolic dysfunction in patients with T2DM.[85] In all, 223 outpatients with T2DM were randomized to supervised exercise-lifestyle intervention or usual care. Patients receiving the intervention were randomized to a two-stage supervised exercise program that comprised an initial four-week gym-based exercise program of two 1-hour exercise sessions per week, supervised by an exercise physiologist, with a further 30 minutes of home-based exercise. Each individualized program sought to provide at least moderate exertion using a combination of both aerobic and resistance exercises. The subsequent home-based program was supported by telephone counseling, with an emphasis on maintenance and improvement. This contact was initially weekly and then once every two weeks for three months, with monthly follow-up thereafter. Patients underwent echocardiographic assessment of diastolic function, metabolic and clinical evaluations at baseline and three years. Diastolic dysfunction was present in 50% of patients at baseline and 54% of patients at three years, with no difference between usual care and intervention groups (60% vs. 48%, $P = 0.10$). Abnormal diastolic function at the final visit was independently associated with older age and a decrease in VO2peak over time ($P < 0.05$). In a sub-analysis restricted to those who finished the full three-year follow-up, control subjects were independently associated with diastolic dysfunction at three years ($\beta = 0.90$, OR = 2.46, $P = 0.034$), with the only other independent correlate being older age ($\beta = 0.05$, OR = 1.06, $P = 0.019$). In this study, three years of exercise-based lifestyle intervention was not effective in reducing progression of subclinical diastolic dysfunction in patients with T2DM.

A recent systematic review to assess the effect of exercise training in patients with HFPEF suggested benefit in terms of enhancements in exercise capacity and health-related QoL, and the exercise training appeared to be safe.[72] The review included studies for a total of 228 individuals, and the combined duration of exercise programs and follow-up ranged from 12 to 24 weeks. No deaths, hospital admissions, or serious adverse events were observed during or immediately following exercise training. Compared to control, the change in exercise capacity at follow-up was higher with exercise training. There was evidence of a larger gain in health-related QoL with exercise training. The largest study included in the review showed some evidence of improvement in the $E/e'$ ratio with exercise training, but this was not confirmed in the other studies; $E/A$ ratios were not changed. Thus, despite the benefit of improved exercise capacity and QoL, the impact on diastolic function remains unclear. Further trials should provide data on long-term effects, prognostic relevance, and cost-effectiveness.[72]

**Cardiac effects.** Exercise training at submaximal levels in HF has no effect on cardiac output[86–88] and slight improvement at peak exercise levels.[77,87] Hambrecht et al.[77], on the other hand, demonstrated reductions in resting left ventricular end-diastolic diameter (LVEDD), suggesting a training-induced reverse remodeling. Furthermore, reduced LV diastolic wall stress even at low–moderate workload (50% VO2peak) has been seen along with a 30% increase in VO2peak after two months.[89] Belardinelli et al.[90] demonstrated improvement in the functional capacity of people with dilated cardiomyopathy and diastolic dysfunction with training. This improvement was, however, limited to people with delayed relaxation. Restrictive cardiomyopathy in this study was associated with a worse prognosis.

**Peripheral effects.** Reversible peripheral abnormalities in HF patients include changes in skeletal muscle and vasomotor tone. Exercise training can improve mitochondrial load with improved oxidative metabolism.[86,91,92] A reverse-shift from type IIb skeletal muscle fibers to type I has also been demonstrated, which is associated with improved exercise capacity.[61] An improved peripheral blood flow and more efficient oxygen delivery have also been seen after exercise training.[88] A beneficial effect on endothelial dysfunction, likely NO mediated as suggested by Hambrecht et al.[77], and endothelium-dependent peripheral blood flow has been associated with improved VO2peak.[76]

Furthermore, messenger ribonucleic acid expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity and reactive oxygen species (ROS) generation responsible for angiotensin II-mediated vasoconstriction has been seen to reduce with exercise.[93,94] A decrease in sympathetic activity has also been demonstrated.[95–98] Reduced levels of the inflammatory cytokines TNF-α and interleukin-6

(IL-6) after training are again associated with an improved exercise capacity.[99,100]

## Exercise Training in HF Patients with Artificial Devices

Exercise training in patients with implantable cardiac devices (ICDs/CRT) has been reported to improve QoL and exercise capacity and seems to be safe.[101] Furthermore, it can also have a positive effect on anxiety in ICD patients and can reduce the fear of exercise.[102–104] Care should, however, be taken for the maximum training HR not to exceed the ICD-intervention HR to avoid any inappropriate shocks. Avoiding a physical trauma to the device, including activities with pronounced arm/shoulder movements, is also sensible.[105] It is recommended that exercise HR reach no higher than 10–15 beats below the ICD tachycardia threshold. Furthermore, upper body resistance exercise should be restricted until six weeks after implantation to prevent dislodgement of newly implanted device leads and healing of the defibrillator site.[14]

## Potential Risks Associated with Exercise Therapy in HF

Exercise training in HF patients is considered safe. Sudden cardiac death (SCD) during exercise is rare in apparently healthy individuals. Individuals with cardiac disease seem to be at a higher risk than healthy individuals. The incidence of major cardiovascular complications during outpatient cardiac exercise programs has been estimated to be 1 in 60,000 participant-hours.[106] Myocardial infarction is another risk associated with participation in exercise and is more likely to occur than SCD. It is highly recommended that a patient should undergo a symptom-limited graded exercise test prior to commencement of exercise training. This test, along with the clinical assessment and measurement of LV function, is used to determine the safety to commence an unmonitored exercise program by excluding myocardial ischemia, determining ischemic thresholds for those in whom complete control of ischemia is not possible, excluding exercise-induced ventricular tachycardia, determining ventricular rate control in patients with atrial fibrillation, assessing functional capacity, and measuring both work rates and HRs at submaximal and maximal levels of exercise.[14] The health professional should be capable of monitoring, managing, and reporting signs and symptoms of worsening HF, excessive shortness of breath or fatigue, and vasovagal signs and symptoms, including bradycardia, excessive sweating, dizziness, confusion, and acute hypotension that may lead to syncope. All adverse events related to exercise must be reported promptly to the primary care medical practitioner or emergency medical personnel.[14]

## Conclusion

Exercise intolerance through various mechanisms is the major incapacitating issue in HF patients, and exercise training programs have shown to improve functional capacity, QoL, dyspnea, as well as HF-related lassitude. Clinical trials have demonstrated a multitude of benefits affecting exercise capacity, metabolic function, vascular tone, cytokine production, and neural activation. Tailored exercise prescription for the modality and intensity, by assessing and interpreting clinical information and applying the principles of training to develop an appropriate regimen, is important to ensure efficiency and safety of the program. Regular exercise results in a modest reduction in risk for clinical events, with even greater benefits likely in patients who adhere to a higher volume of exercise. The impact of exercise training on diastolic function, however, remains less clear as there is inadequate information of long-term outcomes in HFPEF patients, including mortality, hospitalization, and cost-effectiveness. Nevertheless, it appears safe, and further trials in objectively defined HFPEF populations are required.

## Author Contributions

Literature search and review: MAUH, CG. Wrote the first draft of the manuscript: MAUH. Contributed to the writing of the manuscript: CY, IL. Agree with manuscript: IL, CW, DH. Jointly developed the structure and arguments for the paper: MAUH, CY, DH. Made critical revisions and approved final version: CY, DH. All authors reviewed and approved of the final manuscript.

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