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Review

Cardiac Rehabilitation and Heart Failure with Reduced Ejection Fraction: Pathophysiology, Benefits, and Precautions

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ABSTRACT

Heart failure (HF) is a highly comorbid condition associated with significant mortality, despite advances in current medical management. Patients who suffer from HF represent a high needs disease care population in whom structured, long-term chronic disease care delivery models, such as cardiac rehabilitation (CR), have been shown to be highly cost effective in reducing hospitalizations and improving quality of life. HF with reduced ejection fraction affects a growing number of Canadians and health care costs secondary to this condition are increasing, with further increases over the next decade to be expected. CR is a guideline-directed medical therapy for patients living with HF with reduced ejection fraction, and with increasing numbers of HF patients across the world, there is a prescient need to revisit the benefits, safety, and the prescription of this intervention for the health care professionals who treat this condition. Certainly, there is a clinical need for HF practitioners to better understand the pathophysiological benefits of CR with respect to exercise training, as well as the prudent precautions required to facilitate the safe delivery of this highly cost-effective patient intervention.

RÉSUMÉ

L'insuffisance cardiaque (IC) est un trouble hautement comorbide associé à une mortalité importante, malgré les progrès réalisés dans la prise en charge médicale actuelle. Les patients atteints d'IC constituent une population dont les besoins en soins médicaux sont importants, chez qui les modèles structurés de prise en charge à long terme des maladies chroniques, comme la réadaptation cardiaque, se sont avérés très rentables en réduisant les hospitalisations et en améliorant la qualité de vie. L'IC avec fraction d'éjection réduite touche un nombre croissant de Canadiennes et Canadiens, et les coûts en soins de santé associés à ce trouble sont à la hausse et devraient continuer d'augmenter durant la prochaine décennie. La réadaptation cardiaque est une thérapie médicale s'appuyant sur les lignes directrices à la disposition des patients atteints d'IC avec fraction d'éjection réduite. Compte tenu du nombre croissant de patients atteint d'IC dans le monde, il est urgent pour les professionnels de la santé qui traitent cette pathologie de réexaminer les avantages, l'innocuité et les modalités de prescription de cette intervention. Il est évident d'un point de vue clinique que les professionnels qui traitent l'IC doivent mieux comprendre les avantages physiopathologiques de la réadaptation cardiaque, plus particulièrement de l'entraînement par l'exercice, mais aussi les précautions qu'il convient de prendre pour offrir en toute sécurité cette intervention extrêmement rentable aux patients.

Heart failure (HF) is a global health issue associated with significant health care costs and a high rate of hospitalizations. It is estimated that 3.5% of Canadians older than 40 years are suffering from it.[1] Despite being a highly comorbid condition associated with high mortality, improvements in the treatment, subsequently increasing longevity of cardiovascular disease (CVD) patients in recent years, have led to an increase in HF prevalence.[1] Currently, there are more than 787,000 Canadians living with HF, with an average of 111,000 Canadians diagnosed with HF annually.[2] It has one of highest hospital admission rates in Canada and it is anticipated that health care costs secondary to HF might reach CAD$2.8 billion per year by 2030.[2,3] Significant improvements in HF therapeutics and survival aside, many patients still complain of exercise intolerance.[4]

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Cardiac rehabilitation (CR) is recommended as standard care for most persons with documented CVD, including those living with HF.[5] The generally accepted core components of CR for the treatment of patients living with HF with reduced ejection fraction (HFrEF) include appropriate intake assessment and follow-up regarding adherence to guideline-directed medical therapy (GDMT), and are depicted in Figure 1.[6,7] Recent guidelines have emphasized the importance of including physical activity and exercise training in the treatment of patients living with HFrEF. The Canadian Cardiovascular Society in 2017 formulated a strong recommendation for regular exercise in HF patients to improve exercise capacity, symptoms, and quality of life, while decreasing hospital admissions.[8] Likewise, the most recent guidelines from the European Society of Cardiology in 2021[9] and the American Heart Association in 2022[10] strongly endorsed physical activity and regular exercise as a class I recommendation, with CR being a class 2a, in patients living with HFrEF to improve functional capacity, quality of life, and decrease HF hospitalizations. Similarly, in 2022, the Canadian Cardiovascular Harmonization of National Guidelines Endeavour guideline, which ensures the uniform presentation of therapeutic strategies, targets, and clinical practice recommendations across 9 independent CVD professional societies, emphasized the importance of CR as a grade A clinical practice recommendation in patients living with HFrEF.[5]

And yet, despite the strong endorsement from numerous national societies regarding the clinical effectiveness of CR and exercise training in persons living with HFrEF, specific details regarding the optimal method of delivering these interventions remains suboptimal. For example, the ESC 2021 guidelines recommend a supervised exercise-based CR program, allowing that high-intensity interval training (HIIT) in this population might improve peak oxygen consumption (VO_2 max), but without providing any details as to how this strategy is to be executed.[9] What is clearly required are clinical practice guidelines for exercise training and CR for persons living with HFrEF that contain well thought-out, well recognized, and easy to follow treatment algorithms for aerobic training and resistance training, in conjunction with clinical care pathways. The clinical need is no longer to produce greater amounts of epidemiological or population-based research but to develop and disseminate practical tools that will enable health care professionals, including CR health care professionals, to initiate and optimize physical training programs for patients living with HF.

With the increasing burden of HF and the growing need for additional facilities delivering CR worldwide, it is essential to revisit the benefits of this intervention in the HF population. In this review we explore the role of exercise in managing HF, with a focus on its effects with respect to mortality, hospitalizations, safety, and quality of life.

Pathophysiology of Exercise Intolerance in Patients With HF

The mechanisms of exercise intolerance in patients living with HFrEF are complex and not completely understood.[11] It is currently recognized that there is likely an interplay between many mechanisms that cause a decrease in exercise capacity, such as alterations in cardiac function, peripheral blood flow, endothelial (dys)function, vascular and myocyte inflammatory processes, skeletal muscle function, ventilation, and autonomic system regulation.[12] Indeed, the clinically important and beneficial pathophysiologic effects of physical activity and exercise training on vascular inflammation and arterial endothelial dysfunction have long been thought to be at least partially responsible for the improvements in functional capacity in patients with ischemic heart disease and ischemic cardiomyopathy.[13,14] Likely as a consequence of reduced vascular inflammation and the enhanced production (or reduced destruction) of endothelial derived nitric oxide, this enhanced exercise-induced vasodilatation, arguably in the setting of intermittent myocardial ischemia, might enhance cardiac angiogenesis.[8,10]

Along with the putative beneficial effects of exercise training on cardiac angiogenesis mentioned previously, there is some literature to support the theory that improvements in peripheral circulation, along with skeletal muscle function, as a consequence of exercise training in patients with HF, might contribute more to improvements in functional capacity in these patients than their direct effects on cardiac function.[15] Moreover, this theory is supported by the findings of intrinsic anomalies in skeletal muscles of patients with HF compared with inactive patients not suffering from HF. These disturbances are secondary to the long-term physiologic consequences of HF itself, causing sympathetic vasoconstriction, endothelial dysfunction, and chronic elevations in the venous pressures of skeletal muscles, fundamentally altering their function.[16] Aging itself also causes a decrease in aerobic capacity as well as a diminished physiological reserve in all organic systems, further exacerbating the adverse effects of HF therapies by alterations in pharmacokinetic responses, while impairing recovery after hospitalization.[16] As the prevalence of HF increases with age, one could argue that the reduction in functional capacity observed in this population is caused by the additive adverse consequences of aging on fitness in addition to the adverse pathophysiological processes caused by HF.[17] Indeed, it is easy to postulate that the interactive effects of aging and HF on aerobic fitness and functional capacity might be related in an exponential rather than a simply additive fashion.[17]

Finally, reductions in VO_2 max and alterations in hemodynamics are significant contributors to poor exercise capacity in patients with HF. Impairment in oxygen delivery from low cardiac output reserve, restricted capability to increase preload, and abnormal chronotropic reserve, are key features of reduced maximal exercise capacity in this population.[16] Additionally, left ventricular (LV) filling pressures, chronically elevated or abruptly increased during exercise, might lead to an elevation in pulmonary artery pressures that negatively affect right ventricular function, and contribute to the limitation in LV stroke volume augmentation usually observed during exercise.[16] Furthermore, the HF impairments in oxygen extraction induced by alterations in the oxidative capacity of skeletal muscles, in conjunction with alterations in arterial compliance secondary to arterial endothelial dysfunction, might further impair VO_2 max during exercise, as shown by the Fick equation, $VO_2 = SV \times HR \times (a-v\ O_2)$, where, VO_2 = oxygen consumption; SV = stroke volume; HR = heart rate; $a-v\ O_2$ = arterial-venous oxygen content difference.[18-20]

In summary, many factors contribute to the decrease in exercise tolerance observed in patients living with HFrEF but

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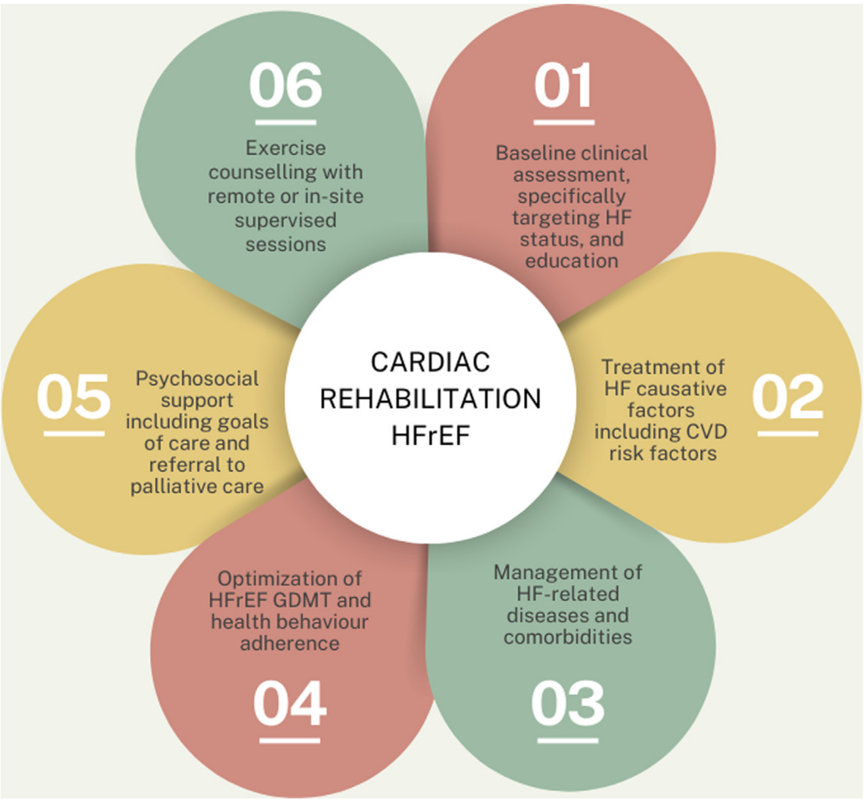

Figure 1. Core elements of cardiac rehabilitation services for patients living with heart failure (HF) with reduced ejection fraction (HFrEF). CVD, cardiovascular disease; GDMT, guideline-directed medical therapy.

aging and the systemic physiologic consequences of HF are key contributors to this reduction.

Role of VO_2 max in Predicting Outcomes

Cardiopulmonary exercise testing (CPET) has been used for many years in the clinical evaluation and risk stratification of HFrEF patients.[21] Peak VO_2 is the gold standard for evaluating exercise tolerance and oxygen delivery during exercise, namely aerobic capacity.[21] Moreover, it is one of the strongest prognostic parameters in patients with HFrEF and is frequently used in determining which HF patients might benefit from cardiac transplantation.[22] Additionally, VO_2 max has a strong correlation with daily walking distance, which can serve as a surrogate in the determination of functional capacity in patients with HF.[23] It has also been reported that improvements in the aerobic capacity of HF patients might lead to better outcomes.[24] Moreover, it is moderately powerful in the assessment of health-related quality of life end points.[25] An abnormal ventilatory response to exercise (minute ventilation [VE]/carbon dioxide production [VCO_2]) during maximal and submaximal CPET has also been described as a poor prognostic factor in patients with normal exercise capacity.[26,27] This observation likely underscores the impairments in oxidative skeletal muscle capacity so frequent in HF patients, which might persist even in those with relatively normal functional capacity. The overall clinical utility of CPET in HFrEF patients is the reason it is the standard test used in many studies of exercise training in this population.[28,29]

Benefits of CR in Patients With HFrEF

In the next sections we review the different possible pathophysiological benefits of exercise training in patients living with HFrEF, which are summarized in Figure 2.

Effect on mortality and hospitalizations

The most impactful randomized clinical trial (RCT) regarding exercise training in HFrEF is the multicentre **H**eart **F**ailure: **A** **C**ontrolled **T**rial **I**nvestigating **O**utcomes of Exercise Trai**n**ing (HF-ACTION) trial published in 2009.[28] This study included 2331 patients living with HFrEF and compared the effects of 36 supervised sessions followed by home-based training vs usual care. After a follow-up of 2.5 years, results showed a nonsignificant reduction in the primary end point (all-cause mortality or hospitalization). However, methodological issues such as poor adherence in the exercise group (up to 30%) and significant crossovers (> 50%) in the usual care group[28] prevent drawing final conclusions about the (in)effectiveness of exercise training on hard outcomes. Importantly, when examining the effects of exercise training on highly prognostic baseline characteristics, there was a significant benefit of exercise training for all-cause mortality or hospitalization and for cardiovascular mortality or HF hospitalization.[28] Interestingly, *post hoc* analysis of this trial showed no significant interaction between HF etiology and treatment for the hard outcomes, nor was there any effect of HF severity or administered treatments on the primary outcomes. This

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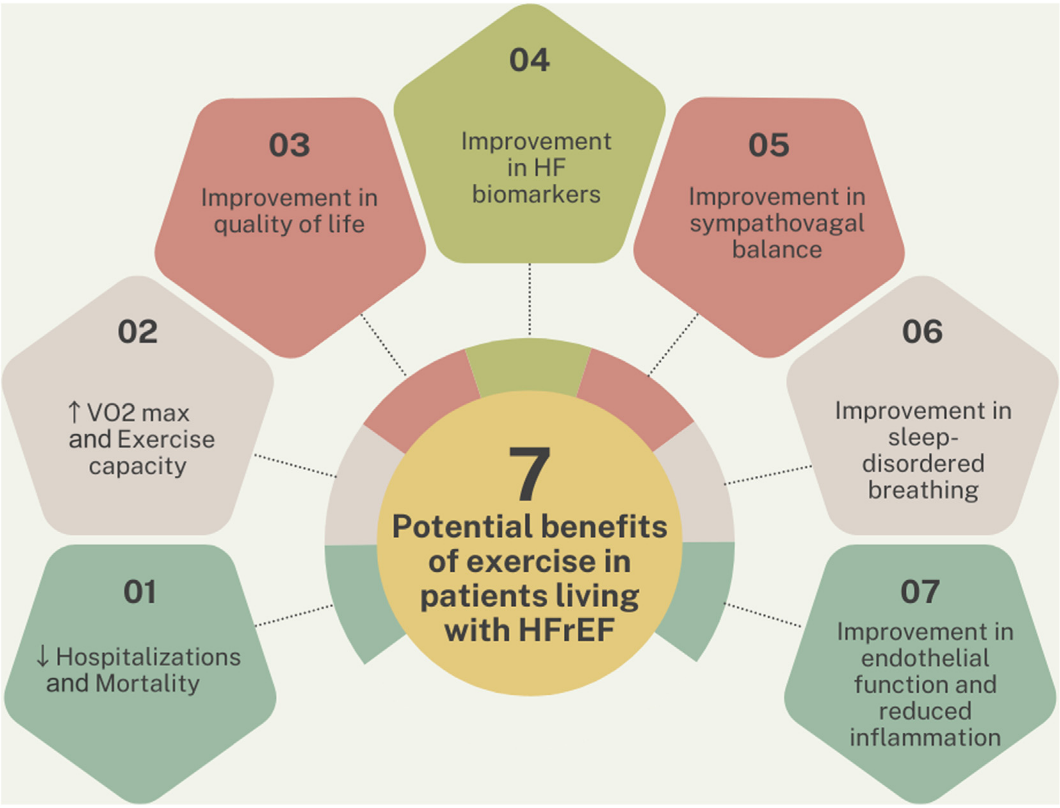

Figure 2. Potential benefits of exercise based cardiac rehabilitation in patients living with heart failure (HF) with reduced ejection fraction (HFrEF). VO2 max, peak oxygen consumption.

emphasizes the importance of considering all patients with HFrEF for CR.[30]

A few earlier researchers in this field reported some positive results of exercise training in decreasing mortality and hospitalization, but patients were not treated with contemporary GDMT and these studies have been highly criticized for methodological flaws.[31,32] Further publications have not reproduced these results. Two meta-analyses showed no significant difference in mortality between the exercise and control groups,[13] but exercise training decreased all-cause hospitalizations and HF-related hospitalizations.[33] However, another meta-analysis showed a trend toward improvement in outcomes if trials extended their follow-up beyond a year.[34]

The benefits of CR in patients with HF have been reviewed in a recent Cochrane analysis.[35] Twenty-seven trials assessed the effect of CR on all-cause mortality over a short-term period and concluded that CR might have a modest or no effect on all-cause mortality. However, within the trials that evaluated exercise training with a follow-up extending beyond a year, CR might improve all-cause mortality. Participation in a CR program led to a number needed to treat of 14 for reductions in overall hospital admissions during short-term follow-up, and a number needed to treat of 25, for a reduction in HF hospitalizations. Moreover, the positive effects of exercise training were shown across different types of CR programs such as hospital vs home-based programs, various doses and types of exercise, and exercise only vs comprehensive programs.[35]

The current literature suggests that not all patients will benefit from CR, although it is not yet clear what factors might play a role in this lack of benefit. It has been shown that the absence of an improvement in physical fitness predicts adverse cardiac events independently of LV ejection fraction (LVEF), New York Heart Association (NYHA) class and brain natriuretic peptide level.[36] Conversely, improvements in oxygen uptake correlated with better outcomes.[24] Moreover, in a meta-analysis that showed lack of improvement in mortality after CR, no interventional effect of exercise was found depending on age, sex, ethnicity, NYHA class, etiology of HF, LVEF, and cardiopulmonary fitness at baseline.[37] A different meta-analysis was not able to identify patient or frailty characteristics predictive of improvement in VO_2 max in patients who underwent CR.[38] Finally, the **Ex**ercise **Tra**ining **M**eta-**A**nalysis of **T**rials in **C**hronic **H**eart Failure II individual patient meta-analysis also did not show any difference in the effect size of CR depending on patient factors.[39]

Nevertheless, nonresponders to CR might be as high as 45%, and this finding was associated with higher all-cause mortality and more hospitalizations.[40] Three different groups of patients are less likely to benefit from rehabilitation: older patients, those with good fitness at baseline (higher VO_2 max), and those with poor adherence.[40] Different methods have been published to address adherence issues in CR with HF patients.[41] A substudy of HF-ACTION showed that poor social support and significant barriers to exercise negatively influenced exercise time, which

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can account for worse outcomes in mortality or hospitalization secondary to HF.[42]

In brief, one could argue that the true potential benefit of exercise has not been proven in HFrEF patients with respect to mortality and hospitalizations, mostly because the current literature does not accurately reflect the poor exercise adherence mentioned in many studies. In addition, none of the trials of exercise-based CR for patients with HFrEF consistently used contemporary GDMT including the use of β-blockers, sodium-glucose transport protein 2 inhibitors, angiotensin receptor/neprilysin inhibitors, or mineralocorticoid receptor antagonists.

Effect on VO_2 max

Many studies over the years have confirmed that different types of exercise training improve exercise capacity, cardiac output, stroke volume, ventricular compliance, and peak VO_2 max in patients with HF.[1,43,44] More specifically, a meta-analysis showed that different types of exercise, namely resistance training, aerobic training, and combined resistance and aerobic training, all lead to improvements in aerobic capacity in HF patients compared with control groups.[45] A small controlled trial quantified this change in HF patients who underwent exercise training for 24 weeks and showed a 16% improvement in VO_2 max as well as improvements in exercise duration and chronotropic incompetence.[46] In the HF-ACTION trial, the supervised exercise sessions improved the 6-minute walk test, the exercise time, and VO_2 max by 4%.[28]

In a systematic review the average increase in VO_2 max after exercise training in HFrEF patients was assessed. The authors reported a mean increment in VO_2 max of 17%: 17% in studies of aerobic training, 9% in studies using only strength training, 15% in studies of combined aerobic and strength training, and 16% for the sole study that included respiratory training.[29]

Interestingly, the improvement in VO_2 max with exercise was more pronounced in HF patients who were taking β-blockers compared with those who were not.[47] Moreover, other researchers have reported that all HF patients responded positively to exercise, including patients with the highest baseline VO_2 (up to 24.4 mL/kg/min), and there was no statistical difference in delta VO_2 after exercise training on the basis of baseline VO_2.[22] However, older patients, those with lower LVEF, and advanced NYHA class might experience a lesser effect on VO_2 max after 12 weeks of training.[22] Nevertheless, most studies did not necessarily correlate improvements in VO_2 with clinical outcomes. This was further studied by Swank et al. in 2012, who demonstrated that an increment in VO_2 max of 6% reduced all-cause mortality or all-cause hospitalization by 5%, decreased the risk of cardiovascular mortality or cardiovascular hospitalization by 4%, decreased the risk of cardiovascular mortality or HF hospitalization by 8%, and reduced all-cause mortality by 7%.[24]

In conclusion, supervised exercise training improves VO_2 max that in turn might improve HF outcomes.

Effect on quality of life

One of the key secondary goals of the HF-ACTION trial was to assess the effects of exercise on quality of life. The exercise training group had a greater improvement than the control group in the **K**ansas **C**ity **C**ardiomyopathy **Q**uestionnaire (KCCQ) score. However, as observed previously, clinically relevant suboptimal adherence in the treatment group might have underestimated the real effect of exercise.[48] Safiyari-Hafizi et al. also reported that quality of life was improved more significantly in patients who underwent a combined home-based program of interval and resistance training than patients who maintained their usual activities.[1] Improvement in quality of life and functional capacity determined according to the 6-minute walk test, were also more significant in a group that underwent aerobic training compared with a control group of patients with HF.[49] Similarly, another study showed that quality of life improved in the exercise, compared with control, group in 4 different domains: physical, psychological, social, and environmental.[50] Meta-analyses have also concluded that there were significant improvements in exercise capacity, as well as improvement in quality of life with physical activity in HFrEF patients.[4,13,34] These results also seem to apply to older, recently discharged patients with decompensated HF, who underwent a CR program.[51]

In short, there is significant evidence that the quality of life in HF patients can be augmented by exercise.

Effect on remodelling, filling pressures, biomarkers, and hemodynamics

Small, mostly observational studies, have assessed the effects of exercise training on remodelling, filling pressures, and sympathovagal balance. A study of patients with HFrEF who underwent exercise training showed a decrease in resting heart rate (HR) values and submaximal HR during exercise without any effect on remodelling parameters or ventricular filling pressures.[52] Another study supports an improvement in peripheral circulation with exercise because patients experienced significant reductions in peripheral resistance associated with reductions in cardiomegaly.[53] Other work also showed an improvement in sympathovagal balance after exercise training with a return to predominantly vagal activity compared with sympathetic activity.[54]

Exercise training seems to improve biomarkers of HF. Supervised training groups had a significant reduction in troponin level at 12 weeks of training along with a decrease in natriuretic peptide values.[55] Moreover, a systematic review showed that aerobic and/or resistance training improved natriuretic peptide values as well.[56]

Other small cohorts of patients with stable HFrEF have shown that exercise training could lead to improvements in LV volumes and LVEF compared with control groups, while exercise capacity improved as well.[15,57,58] Other studies showed that aerobic exercise could lead to reverse LV remodelling.[59,60] Interestingly, a small study revealed that exercise training might have the same positive effect as resynchronization therapy in selected patients.[61]

In summary, exercise training improves HF biomarkers and sympathovagal balance, although its effects on cardiac function are less clear.

Effects on systemic inflammation

Elevated CRP is an independent adverse prognostic biomarker in HF.[62] Physical activity has been shown to have an

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inverse relationship with inflammatory biomarkers, in the general population,[63] as well as in HFrEF patients. In a small study of patients with stable HFrEF, inflammatory markers (CRP, TNF-α, ICAM-1, and vascular cell adhesion molecule 1) were significantly reduced after a CR intervention.[14] The magnitude of the reduction in these inflammatory markers depended on the type, intensity, and duration of the CR program.[14] However, a systematic review and meta-analysis concluded that exercise training in patients living with HFrEF might have a minimally favourable effect on reducing TNF-α levels but did not indicate any strong evidence to support reductions in other inflammatory markers.[64] The dose of exercise in these RCTs was extremely variable, from 10 minutes 2 days per week to 90 minutes up to 7 days per week, which might provide clinical insight into the apparent (in) effectiveness.[64]

Effects on sleep health

Sleep-disordered breathing, specifically central apnea, is well documented in patient with HF and adversely alters the long-term prognosis of these patients.[65] A small cohort of patients with sleep-disordered breathing underwent exercise-based CR for 6 months and, compared with the control group, experienced a significant reduction in their apnea-hypopnea index.[66] Interestingly, CR only reduced the episodes of central sleep apnea and did not affect the number of obstructive episodes.

Effects on skeletal muscle function

Intrinsic skeletal muscle dysfunction is another fundamental metabolic mechanism of reduced exercise capacity in patients living with HFrEF. A 4-week exercise training RCT, which included healthy persons and patients living with HFrEF, reduced muscle ring finger-1 mRNA expression, thought to be involved in muscle wasting, by 33% in the HFrEF patients 55 years old and younger, and by 37% in those 65 years old and older.[17] The mechanisms responsible for these types of improvements in skeletal muscle mass and function might also include improvements in skeletal muscle microcirculation, control of mitochondria, favourable alterations in muscle fibre composition, enhanced oxidative metabolic capacity, and intracellular oxygen transport.[67]

The ability of skeletal muscle to respond to exercise in patients with HF might be further compromised by pathophysiologic maladaptation during exercise with preferential redirection of blood flow of locomotor muscles to accommodate the work of breathing.[68] This likely results in a more rapid onset of anaerobic metabolism and oxygen debt, further reducing functional capacity.

Effects on endothelial dysfunction

HFrEF might promote vascular endothelial (dys)function by reducing the availability of endothelium-derived nitric oxide and increasing the synthesis of reactive oxygen species that increase vascular inflammation.[69] A small cohort of HFrEF patients who underwent different types of training, had significantly reduced levels of serum vascular cell adhesion molecules after a 10-week exercise program.[70]

Exercise can also improve endothelial (dys)function, which in turn might improve ventricular-vascular coupling and outcomes in persons living with HFrEF.[71] A meta-analysis of the effects of exercise training on endothelial function in HF patients showed improvement in endothelial function, assessed using flow-mediated dilatation.[72] Thus, improvements in endothelial (dys)function in the setting of HFrEF, through exercise training, might reduce vascular inflammation, improve ventricular-vascular coupling and, in turn, improve functional capacity, and potentially, clinical outcomes.[73]

Safety of CR in Patients With HFrEF

Among all of the multiple publications in this field, no study has ever shown concerns about the safety of exercise training in HFrEF patients. A Cochrane review published in 2019 does not mention any signals of possible harm with this intervention in HFrEF patients.[35] HF-ACTION is the largest published trial to date concerning exercise in stable HF patients treated with contemporary optimized GDMT. Despite the inclusion of patients with advanced HF, exercise was safe and there was no difference in adverse events between the exercise and the usual care groups.[28] In a systematic review the safety of this treatment was analyzed with more than 60,000 patient-hours of exercise training within 81 studies. There were no reports of mortality directly related to exercise and there were fewer combined adverse events ($n = 19$) in the exercise group compared with the control group during the training and follow-up periods.[29]

Evidence is slowly growing that early CR in patients with acute decompensated HF might also be safe. The Physical **REHAB**ilitation for Older Patients Hospitalized for **H**eart **F**ailure trial included older HF patients, with multiple comorbidities, frail, and with altered physical capacity. A stepwise, individualized CR program initiated during hospitalization and pursued for 12 weeks after discharge was safe and led to significant improvements in physical function and reduced the number of rehospitalizations for any cause.[74] The **E**jection **J**oins **E**ducation: **C**ombined **T**herapy to **I**mprove **O**utcomes in **N**ewly-discharged **H**eart **F**ailure trial concluded that combining a 24-week supervised hospital-based exercise training program with a multidisciplinary HF management program in patients with HFrEF and HF with preserved ejection fraction (HFpEF) was safe, although it did not improve the combined outcome of mortality and rehospitalizations compared with a HF management program alone. Nevertheless, patients aged younger than 70 years or those who showed adherence to the training program had lower combined outcome of mortality and rehospitalizations.[75] The most obvious and robust endorsement regarding the safety of moderate to vigorous physical activity, including vigorous HIIT, in patients living with HFrEF, comes from several national CVD guidelines and expert statements, reinforcing the clinical evidence to support this recommendation.[9,11,76]

Ideally, all CR programs should be staffed and administered by a group of multidisciplinary health care professionals who are familiar and comfortable with patients living with HFrEF. Although patient safety in this population has been repeatedly reported, there is no denying that a significant portion of that safety derives from a highly experienced group of health care professionals supplying supervised CR programs.[9,11,76]

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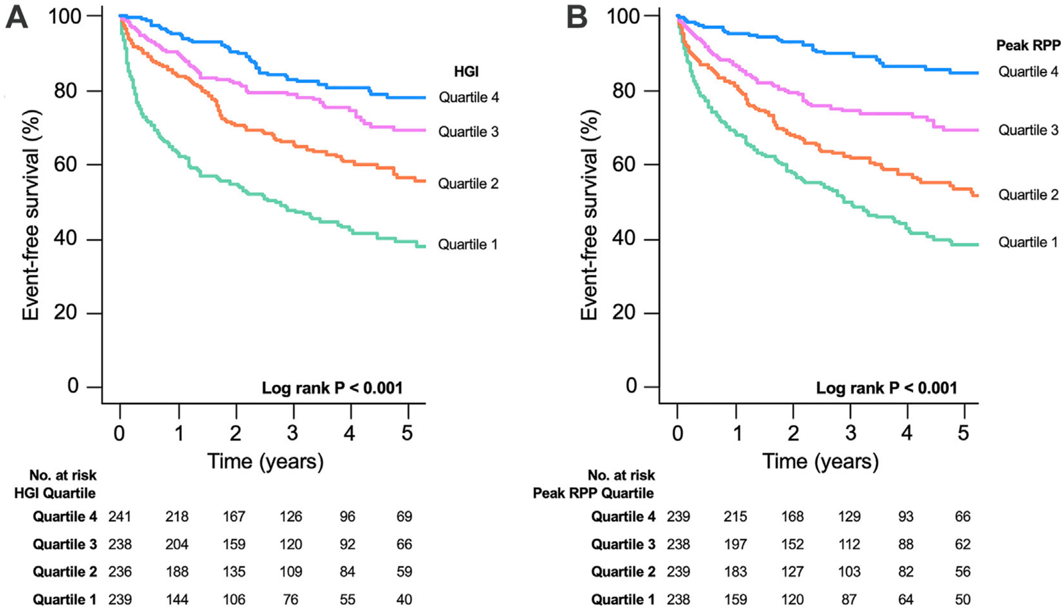

Figure 3. Kaplan-Meier curves show event-free survival, over 5 years, in patients living with heart failure with reduced ejection fraction stratified according to heart gain index (HGI) and rate pressure product (RPP). Reproduced from Chaikijurajai et al.[85] with permission from Elsevier.

Optimal Training Methods

Despite numerous publications that have assessed different types of exercise in patients with HF, the optimal training method is yet to be identified. One of the most significant issues is the heterogeneity of all of the trials published to date. A recent systematic review showed that exercise intensity was the parameter most often missing in the exercise programs of the trials.[77] Moreover, most of them did not explore motivational strategies or a home-based approach in their CR program, and adherence to exercise training is frequently not mentioned. Unfortunately, contemporary trials are not better at reporting their exercise program details compared with older studies.[77] However, although there is still uncertainty about the best CR program exercise prescription, the most important message is to exercise. The benefits of CR have been proven to be unrelated to the type and dose of exercise training as well as the duration of follow-up.[34] A small RCT showed that allowing HFrEF patients to choose their own physical training program resulted in better long-term maintenance of physical activity at 1 year follow-up.[78]

In the next sections we summarize the known literature about different components of CR programs for patients with HF.

Prescription of exercise

CR societies recommend an initial exercise test as a mandatory assessment of functional capacity, with CPET being the gold standard for direct evaluation of the different exercise thresholds because it allows for a more robust exercise prescription on the basis of first and second ventilatory threshold.[6,76,79] However, there has been a paradigm shift from previous guidelines that recommended a fixed zone-based exercise prescription on the basis of ventilatory thresholds[79] to a more liberal intensity prescription of exercise on the basis of %VO_2 max in the current literature.[80] A recent study has shown that the ventilatory thresholds are often not identifiable on many cardiopulmonary exercise tests, despite offering a more powerful exercise-based prescription, because exercise intensity on the basis of %VO_2 max and/or peak HR differs significantly between subjects known with CVD.[81] Also, some key components of CPET must be interpreted with caution in patients living with HFrEF, because a plateau of VO_2 max might not be measured in this population; one should then ensure the test is on the basis of maximal effort and on respiratory exchange ratio.[82] HF GDMT, cardiac resynchronization, age, and sex might also affect VO_2 max.[21,82] Some experts recommend that the exercise regimen should be prescribed at HRs corresponding to 50%-75% VO_2 max, although 40%-50% VO_2 max might be more appropriate for patients with severe functional impairment.[82,83] Moreover, it is still unknown if the prescription should be revisited in cases of multifactorial noncardiac limitations to exercise, which cause a significant baseline decrease in functional capacity and exercise tolerance.[12] Therefore, further cohort studies of patients living with HFrEF are needed to ascertain which method (zone-based vs intensity-based on % VO_2 and/or HR) is superior to improve exercise capacity, and consequently improve outcomes in this population.

CPET is not a resource available in all CR facilities to allow appropriate exercise prescription.[84] A recent study that included patients living with HFrEF, mostly treated with β-blockers, showed that using peak rate pressure product had a good correlation with VO_2 max in terms of predicting outcomes (Fig. 3).[85] This observation reinforces the clinical utility of data obtained from a standard exercise treadmill test for exercise prescription instead of using CPET in all patients. Therefore, exercise prescription intensity in CR facilities is generally on the basis of a HR derived from the linear relationship between HR, VO_2 max, and work rate.[79,83] A HR

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reserve of 40%-80%, maximum HR 65%-85%,[83] is generally recommended for a moderate continuous training (MCT),[76,80] for 20-60 minutes per session ideally on most days of the week.[76,83] The use of a HR target for exercise prescription might pose significant challenges for patients living with HFrEF, because their HR response might not be reliable, and might therefore not adequately represent their intensity of training.[79] In addition, using this method is usually not well suited for a home-based program and long-term exercise prescription. The rate of perceived exertion, although subjective, has been shown to be a valid method of exercise prescription in a small cohort of HF patients, and led to the same physiologic adaptations as the HR-based exercise prescription.[86] A rate of perceived exertion variating between 3 and 14, attesting the uncertainty in the literature of the appropriate method of exercise prescription in this population, is considered an adjunct to the objective measurement of HR in patients living with HFrEF.[76,83]

Home-based vs hospital-based program

The literature supports that home-based programs are safe, but supervision is a key factor for improvements. Concerns have been raised about the adherence of patients who undertake a home-based CR program because their physical capacity did not improve after 9 months of follow-up.[43] Moreover, a single-centre observational study that compared patients with in-hospital supervised sessions vs patients with home training after education with a physiotherapist only, showed that VO_2 max and quality of life only improved in the supervised group during follow-up.[87] However, a meta-analysis that compared outpatient supervised exercise training vs usual care showed that supervised home-based programs were safe and efficient, because patients improved their VO_2 max, 6-minute walking test, and quality of life compared with the usual care group.[88] Finally, a small cohort of patients randomized to supervised exercise training, either hospital-based or home-based, showed improvements without significant differences in VO_2 max, 6-minute walk test, and LVEF in both groups.[89] Hence, some form of supervision is key.

HIIT vs MCT

Despite multiple trials in the literature that have compared both types of exercise training, controversies remain as to whether HIIT or MCT deliver more clinical benefits, although the former has definitively gained evidence of clinical benefits over MCT in recent publications.[90,91] Of note, most patients were receiving β-blockers in these trials that compared HIIT with MCT, although this has not been reported systemically in meta-analysis. Superiority of aerobic HIIT over MCT has been reported in a small RCT of older HFrEF patients, in terms of improvement in VO_2 max and reversal of LV remodelling.[19] A meta-analysis showed the superiority of supervised HIIT over MCT in the degree of improvement in VO_2 max, although patients tended to be younger and predominantly male.[92] The effect of both types of training on LVEF was not conclusive, but HIIT was safe and led to similar adherence as with MCT.[92] Greater improvement in VO_2 max without a significant difference in VE/VCO_2 slope and quality of life was also shown in a more recent published meta-analysis that compared both types of training. However, if isocaloric protocols were used, no differences were observed.[91]

Other studies have established an absence of benefits between either type of training. In a small observational study of HF patients recently diagnosed with ischemic cardiomyopathy, MCT vs HIIT did not result in any differences in VO_2 max or changes in cardiac function.[93] In a small cohort of patients who underwent a CR program, MCT improved early HR reserve compared with HIIT, which favoured an overall improvement in the autonomic system with an increase in parasympathetic activity. Nevertheless, both types of training improved exercise capacity.[94] Finally, Ellingsen et al. reported the equivalence of both types of training in terms of ventricular remodelling and exercise capacity.[95] However, an important limitation in this study was the adherence to HR targets in each training group in that half of the patients in the HIIT group exercised below their target HR and 80% in the MCT group exercised above it. Hence, no definitive conclusions can be made from this study.[95]

Resistance training

The positive effects of resistance training have been documented in the literature for patients living with HFrEF. Publications to date generally support its safety, resulting in better outcomes when used in combination with aerobic training. A Canadian RCT showed the superiority of a combination of aerobic and resistance training in HF patients.[96] In patients with optimal adherence, the aerobic and combined aerobic with resistance training groups had an increment in aerobic capacity compared with usual care. The combined training was the best method of exercise to enhance muscle strength and endurance, whereas aerobic training alone was the one leading to the greatest increase in VO_2 max.[96] A small cohort of patients showed improvements in their confidence toward exercise and a reduction in their HF symptoms with combined aerobic and resistance training compared with the control group.[97] Another small prospective study showed the superiority of combined aerobic training with resistance training and inspiratory muscle training over aerobic training alone in terms of quadriceps strength and endurance, exercise time, VO_2 max, exercise tolerance, and quality of life.[98] Another trial led to the same conclusions; combined endurance-resistance training vs endurance training alone in HFrEF patients resulted in an enhanced workload, decreased HR, and improved quality of life.[99] Similar results were found in a small cohort of men with HFrEF; the combination of both training techniques was better at increasing LVEF, VO_2 max, and muscle strength compared with endurance training alone.[100]

Other studies have not been able to prove the benefits of combined training over regular aerobic training. A meta-analysis published in 2018 reported on benefits of resistance training on VO_2 max without causing any harm to cardiac function itself. However, there were no differences in oxygen uptake between resistance training, aerobic training, or a combination of both.[45] Similar conclusions were drawn in a study that compared these 3 different methods of training in HFrEF patients. No differences were reported between groups with regard to LVEF, VO_2 max, peak workload, muscle strength, endurance, and quality of life.[101]

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Short- vs long-term exercise training

Although the studies mentioned so far have shown that different types and settings of exercise training led to clinical benefits, the literature suggests that patients have better outcomes if they can maintain long-term exercise training. A small cohort of patients with advanced HF underwent a supervised CR program with follow-up extended up to 3 years. Less than half of the patients discontinued the exercise program after an average of 2 years resulting in a mortality rate of 20%, whereas the other half that maintained the program for the entire duration were all alive at follow-up.[102] Additional inspection of Figure 3 will also show evidence that suggests that the persons living with HFrEF with the highest functional capacity, when maintained over time, have the best absolute and relative survival over time, providing additional evidence in favour of long-term adherence to exercise training.[85]

Gaps and Barriers in Current Practice

The benefits of CR in patients with HFrEF have been well demonstrated without evidence of significant adverse effects. Therefore, there is an urgent need to adopt standard CR care that incorporates MCT and/or HIIT for HF patients, along with resistance training to improve outcomes in this highly comorbid population. Health care payers and providers need to avoid failing at HF therapy when it comes to CR.[103]

Although not addressed in this review article, prevalence of HFpEF is rising rapidly.[104] The clinical risk factors associated with its development are related to the promoters of systemic inflammation and metabolic stress. The American Heart Association/American College of Cardiology advisory regarding the clinical utility of supervised exercise training for this population states that, in addition to exercise training, chronic disease care strategies in this population will also need to emphasize therapeutic interventions that minimize systemic inflammation and metabolic stress from the comorbid diseases substantially increasing the incidence of HFpEF.[105] Therefore, chronic disease care programs such as CR and comprehensive, coordinated clinical practice guidelines such as those from the Canadian Cardiovascular Harmonization of National Guidelines Endeavour are optimally situated to minimize the clinical and economic consequences of this disease process, and potentially reduce its incidence and prevalence.[5]

And yet, with regard to the current capacity of CR programs in Canada to absorb this population, a recent Canadian survey published in 2018 showed the gap between each province in terms of CR facilities and the insufficient CR capability across Canada.[106] Unfortunately, limited CR availability is a worldwide concern. In a survey published in 2019 completed in 203 countries, only 54.7% had CR programs, with a mean number of 246 patients a program could serve annually, this represented 1 CR spot per 11 eligible cases.[107]

Including CR in the treatment of HFrEF is cost-effective. An analysis has been conducted in a Cochrane review and showed that by subtracting the hospitalization from the rehabilitation costs, there was an extra mean cost of USD$3227 per patient, that was positively overcome by the gain in survival with exercise, leading to a highly improved cost-effectiveness ratio of $USD1773 per life-year saved.[35] The comparative effectiveness of the core components of CR on mortality and morbidity was examined in a systematic review/meta-analysis published in 2018.[108] There was a trend toward effectiveness of risk factor modification, psychological management, and patient education on outcomes. Nutritional counselling did not show a positive effect on morbidity and mortality, whereas exercise training showed a statistically significant benefit in the general CR population. However, a meta-analysis showed that supervised exercise training might be cost-effective in only 55% of patients,[109] at least with respect to inpatient exercise supervision. Nonetheless, it is possible to reasonably hypothesize that exercise training, adherence to GDMT, atherosclerotic CVD risk factor management, mental health interventions, and patient education all provided with CR programs is likely to be cost-effective in this population, on the basis of observations derived from the general CR population. But, unlike the general CR population in whom nutritional counselling did not seem to have a significant benefit on clinical outcomes, the importance of reduced salt intake and caloric modulation in the HF population might indeed prove cost-effective. A clinical trial in this area is desperately required.

Conclusions

CR in patients living with HFrEF significantly improves exercise capacity and quality of life and might have benefits on survival and subsequent hospitalizations. Even though the optimal exercise program is not presently known, HF patients' outcomes will likely be positively influenced by doing the most exercise they can. Currently, there are not enough CR facilities worldwide to meet the demand for this highly cost-effective intervention among this population, and coverage issues need to be addressed to ensure that all patients have access to this beneficial intervention. Although the current scientific evidence supports the systematic inclusion of these patients in CR programs, further studies are required to determine which subgroups of patients might benefit even more from this intervention. Moreover, there is growing evidence about the benefits of CR in patients with HFpEF,[105,110] which will likely become an approved indication for CR in the coming years. Therefore, it is crucial to ensure HFrEF patients are already well cared for in CR programs in the world.

Furthermore, there is an urgent need for professional societies to develop evidence-based, but practical and efficient, treatment algorithms for the administration of exercise training, in conjunction with titration of GDMT, in this population. Ideally, patients who are interested in participating in moderate to vigorous exercise should be referred to their local CR program. However, the clinical reality is that on a worldwide basis, such expertise is not available within a reasonable geographic area. Accessing these services virtually is becoming increasingly possible. Indeed, risk stratification tools such as the ePARmed-X+ patient questionnaire (eparmedx.com) might prove invaluable to small centres where expertise in the provision of CR and exercise training, in conjunction with the clinical management of HF, is less robust. The use of these types of risk stratification screening tools has the potential to significantly increase the number of persons living with HFrEF who will participate in regular

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physical activity and will do so in as safe an environment as is realistically attainable. Patients living with HFrEF need far fewer, not more, barriers to incorporating physical activity and exercise into their HF management strategies.

Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a review article using already published literature, and therefore did not require consent from the patients.

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References

1. Safiyari-Hafizi H, Taunton J, Ignaszewski A, Warburton DE. The Health benefits of a 12-week home-based interval training cardiac rehabilitation program in patients with heart failure. Can J Cardiol 2016;32:561-7.

2. Moghaddam N, Lindsay MP, Hawkins NM, et al. Access to heart failure services in Canada: findings of the Heart and Stroke National Heart Failure Resources and Services Inventory. Can J Cardiol 2023;39:1469-79.

3. Tran DT, Ohinmaa A, Thanh NX, et al. The current and future financial burden of hospital admissions for heart failure in Canada: a cost analysis. CMAJ Open 2016;4:E365-70.

4. van Tol BA, Huijsmans RJ, Kroon DW, Schothorst M, Kwakkel G. Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: a meta-analysis. Eur J Heart Fail 2006;8:841-50.

5. Jain R, Stone JA, Agarwal G, et al. Canadian Cardiovascular Harmonized National Guideline Endeavour (C-CHANGE) guideline for the prevention and management of cardiovascular disease in primary care: 2022 update. [erratum in: 2022;194:E1694]. CMAJ 2022;194:E1460-80.

6. Stone JA, Arthur HM; Canadian Association of Cardiac Rehabilitation Guidelines Writing Group. Canadian Guidelines for cardiac rehabilitation and cardiovascular disease prevention, second edition, 2004: executive summary. CJC 2005;21:3D-19D.

7. Corrà U, Giannuzzi P, Adamopoulos S, et al. Executive summary of the position paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology (ESC): core components of cardiac rehabilitation in chronic heart failure. Eur J Cardiovasc Prev Rehabil 2005;12:321-5.

8. Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure. Can J Cardiol 2017;33:1342-433.

9. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2022;24:4-131.

10. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2022;79:e263-421.

11. Downing J, Balady GJ. The role of exercise training in heart failure. J Am Coll Cardiol 2011;58:561-9.

12. Morris JH, Chen L. Exercise training and heart failure: a review of the literature. Card Fail Rev 2019;5:57-61.

13. Davies EJ, Moxham T, Rees K, et al. Exercise training for systolic heart failure: Cochrane systematic review and meta-analysis. Eur J Heart Fail 2010;12:706-15.

14. Papathanasiou JV, Petrov I, Tsekoura D, et al. Does group-based high-intensity aerobic interval training improve the inflammatory status in patients with chronic heart failure? Eur J Phys Rehabil Med 2022;58:242-50.

15. Giannuzzi P, Temporelli PL, Corrà U, Tavazzi L; ELVD-CHF Study Group. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure: results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) trial. Circulation 2003;108:554-9.

16. Fleg JL, Cooper LS, Borlaug BA, et al. Exercise training as therapy for heart failure: current status and future directions. Circ Heart Fail 2015;8:209-20.

17. Gielen S, Sandri M, Kozarez I, et al. Exercise training attenuates MuRF-1 expression in the skeletal muscle of patients with chronic heart failure independent of age: the randomized Leipzig Exercise Intervention in Chronic Heart Failure and Aging catabolism study. Circulation 2012;125:2716-27.

18. Kitzman DW, Brubaker PH, Herrington DM, et al. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. J Am Coll Cardiol 2013;62:584-92.

19. Wisløff U, Støylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation 2007;115:3086-94.

20. Dhakal BP, Malhotra R, Murphy RM, et al. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. Circ Heart Fail 2015;8:286-94.

21. Corrà U, Agostoni PG, Anker SD, et al. Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology [erratum in: 2018;20:1501]. Eur J Heart Fail 2018;20:3-15.

22. Karlsen T, Videm V, Halle M, et al. Baseline and exercise predictors of VO2peak in systolic heart failure patients: results from SMARTEX-HF. Med Sci Sports Exerc 2020;52:810-9.

23. Jehn M, Schmidt-Trucksäss A, Schuster T, et al. Daily walking performance as an independent predictor of advanced heart failure: prediction of exercise capacity in chronic heart failure [erratum in: 2009;157:635]. Am Heart J 2009;157:292-8.

24. Swank AM, Horton J, Fleg JL, et al. Modest increase in peak VO2 is related to better clinical outcomes in chronic heart failure patients:

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results from heart failure and a controlled trial to investigate outcomes of exercise training. Circ Heart Fail 2012;5:579-85.

25. Ciani O, Piepoli M, Smart N, et al. Validation of exercise capacity as a surrogate endpoint in exercise-based rehabilitation for heart failure: a meta-analysis of randomized controlled trials. JACC Heart Fail 2018;6: 596-604.
26. Segreti A, Verolino G, Crispino SP, Agostoni P. Listing criteria for heart transplant: role of cardiopulmonary exercise test and of prognostic scores. Heart Fail Clin 2021;17:635-46.
27. Ponikowski P, Francis DP, Piepoli MF, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. Circulation 2001;103:967-72.
28. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439-50.
29. Smart N, Marwick TH. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. Am J Med 2004;116:693-706.
30. Whellan DJ, Nigam A, Arnold M, et al. Benefit of exercise therapy for systolic heart failure in relation to disease severity and etiology-findings from the Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training study. Am Heart J 2011;162:1003-10.
31. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation 1999;99:1173-82.
32. Piepoli MF, Davos C, Francis DP, Coats AJ. ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ 2004;328:189.
33. Taylor RS, Long L, Mordi IR, et al. Exercise-based rehabilitation for heart failure: Cochrane systematic review, meta-analysis, and trial sequential analysis. JACC Heart Fail 2019;7:691-705.
34. Sagar VA, Davies EJ, Briscoe S, et al. Exercise-based rehabilitation for heart failure: systematic review and meta-analysis. Open Heart 2015;2: e000163.
35. Long L, Mordi IR, Bridges C, et al. Exercise-based cardiac rehabilitation for adults with heart failure. Cochrane Database Syst Rev 2019;1: CD003331.
36. Tabet JY, Meurin P, Beauvais F, et al. Absence of exercise capacity improvement after exercise training program: a strong prognostic factor in patients with chronic heart failure. Circ Heart Fail 2008;1:220-6.
37. Taylor RS, Walker S, Smart NA, et al. Impact of exercise rehabilitation on exercise capacity and quality-of-life in heart failure: individual participant meta-analysis. J Am Coll Cardiol 2019;73:1430-43.
38. Uddin J, Zwisler AD, Lewinter C, et al. Predictors of exercise capacity following exercise-based rehabilitation in patients with coronary heart disease and heart failure: a meta-regression analysis. Eur J Prev Cardiol 2016;23:683-93.
39. Taylor RS, Walker S, Smart NA, et al. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. Eur J Heart Fail 2018;20:1735-43.
40. Bakker EA, Snoek JA, Meindersma EP, et al. Absence of fitness improvement is associated with outcomes in heart failure patients. Med Sci Sports Exerc 2018;50:196-203.
41. Conraads VM, Deaton C, Piotrowicz E, et al. Adherence of heart failure patients to exercise: barriers and possible solutions: a position statement of the Study Group on Exercise Training in Heart Failure of the Heart Failure Association of the European Society of Cardiology [erratum in: 2012;14:802]. Eur J Heart Fail 2012;14:451-8.
42. Cooper LB, Mentz RJ, Sun JL, et al. Psychosocial factors, exercise adherence, and outcomes in heart failure patients: insights from Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) [erratum in: 2016;9:e000014]. Circ Heart Fail 2015;8: 1044-51.
43. McKelvie RS, Teo KK, Roberts R, et al. Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT). Am Heart J 2002;144:23-30.
44. Huang SC, Wong MK, Lin PJ, et al. Modified high-intensity interval training increases peak cardiac power output in patients with heart failure. Eur J Appl Physiol 2014;114:1853-62.
45. Santos FV, Chiappa GR, Ramalho SHR, et al. Resistance exercise enhances oxygen uptake without worsening cardiac function in patients with systolic heart failure: a systematic review and meta-analysis. Heart Fail Rev 2018;23:73-89.
46. Keteyian SJ, Levine AB, Brawner CA, et al. Exercise training in patients with heart failure. A randomized, controlled trial. Ann Intern Med 1996;124:1051-7.
47. Ismail H, McFarlane JR, Nojoumian AH, Dieberg G, Smart NA. Clinical outcomes and cardiovascular responses to different exercise training intensities in patients with heart failure: a systematic review and meta-analysis. JACC Heart Fail 2013;1:514-22.
48. Flynn KE, Piña IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial [erratum in: 2009;302:2322]. JAMA 2009;301:1451-9.
49. Nilsson BB, Westheim A, Risberg MA. Effects of group-based high-intensity aerobic interval training in patients with chronic heart failure. Am J Cardiol 2008;102:1361-5.
50. Bocalini DS, dos Santos L, Serra AJ. Physical exercise improves the functional capacity and quality of life in patients with heart failure. Clinics (Sao Paulo) 2008;63:437-42.
51. Kitzman DW, Whellan DJ, Duncan P, et al. Physical rehabilitation for older patients hospitalized for heart failure. N Engl J Med 2021;385: 203-16.
52. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction. Hemodynamic and metabolic effects. Circulation 1988;78:506-15.
53. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: a randomized trial. JAMA 2000;283:3095-101.
54. Coats AJ, Adamopoulos S, Radaelli A, et al. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. Circulation 1992;85:2119-31.
55. Riveland E, Valborgland T, Ushakova A, et al. Exercise training and high-sensitivity cardiac troponin-I in patients with heart failure with reduced ejection fraction. ESC Heart Fail 2024;11:1121-32.
56. Smart NA, Steele M. Systematic review of the effect of aerobic and resistance exercise training on systemic brain natriuretic peptide (BNP) and N-terminal BNP expression in heart failure patients. Int J Cardiol 2010;140:260-5.

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57. Haykowsky MJ, Liang Y, Pechter D, et al. A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed. J Am Coll Cardiol 2007;49:2329-36.

58. Alves AJ, Ribeiro F, Goldhammer E, et al. Exercise training improves diastolic function in heart failure patients. Med Sci Sports Exerc 2012;44:776-85.

59. Höllriegel R, Winzer EB, Linke A, et al. Long-term exercise training in patients with advanced chronic heart failure: sustained benefits on left ventricular performance and exercise capacity. J Cardiopulm Rehabil Prev 2016;36:117-24.

60. Chen YM, Li ZB, Zhu M, Cao YM. Effects of exercise training on left ventricular remodelling in heart failure patients: an updated meta-analysis of randomised controlled trials. Int J Clin Pract 2012;66:782-91.

61. Smolis-Bąk E, Chwyczko T, Kowalik I, et al. Exercise training program in patients with NYHA III class systolic heart failure - parallel comparison to the effects of resynchronization therapy. Adv Med Sci 2019;64:241-5.

62. Dupuy AM, Curinier C, Kuster N, et al. Multi-marker strategy in heart failure: combination of ST2 and CRP predicts poor outcome. PLoS One 2016;11:e0157159.

63. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. J Am Coll Cardiol 2005;45:1563-9.

64. Pearson MJ, Mungovan SF, Smart NA. Effect of aerobic and resistance training on inflammatory markers in heart failure patients: systematic review and meta-analysis. Heart Fail Rev 2018;23:209-23.

65. Emdin M, Mirizzi G, Giannoni A, et al. Prognostic significance of central apneas throughout a 24-hour period in patients with heart failure. J Am Coll Cardiol 2017;70:1351-64.

66. Yamamoto U, Mohri M, Shimada K, et al. Six-month aerobic exercise training ameliorates central sleep apnea in patients with chronic heart failure. J Cardiac Fail 2007;13:25-829.

67. Hirai DM, Musch TI, Poole DC. Exercise training in chronic heart failure: improving skeletal muscle O2 transport and utilization. Am J Physiol Heart Circ Physiol 2015;309:H1419-39.

68. Olson TP, Joyner MJ, Dietz NM, et al. Effects of respiratory muscle work on blood flow distribution during exercise in heart failure. J Physiol 2010;588:2487-501.

69. Drera A, Rodella L, Brangi E, Riccardi M, Vizzardi E. Endothelial dysfunction in heart failure: what is its role? J Clin Med 2024;13:2534.

70. Aksoy S, Findikoglu G, Ardic F, Rota S, Dursunoglu D. Effect of 10-week supervised moderate-intensity intermittent vs. continuous aerobic exercise programs on vascular adhesion molecules in patients with heart failure. Am J Phys Med Rehabil 2015;94(10 suppl 1):898-911.

71. Pearson MJ, Smart NA. Effect of exercise training on endothelial function in heart failure patients: a systematic review meta-analysis. Int J Cardiol 2017;231:234-43.

72. Fuertes-Kenneally L, Manresa-Rocamora A, Blasco-Peris C, et al. Effects and optimal dose of exercise on endothelial function in patients with heart failure: a systematic review and meta-analysis. Sports Med Open 2023;9:8.

73. Pugliese NR, Balletti A, Armenia S, et al. Ventricular-arterial coupling derived from proximal aortic stiffness and aerobic capacity across the heart failure spectrum. JACC Cardiovasc Imaging 2022;15:1545-59.

74. Reeves GR, Whellan DJ, O'Connor CM, et al. A novel rehabilitation intervention for older patients with acute decompensated heart failure: the REHAB-HF pilot study. JACC Heart Fail 2017;5:359-66.

75. Mudge AM, Denaro CP, Scott AC, et al. Addition of supervised exercise training to a post-hospital disease management program for patients recently hospitalized with acute heart failure: the EJECTION-HF randomized phase 4 trial. JACC Heart Fail 2018;6:143-52.

76. American Association of Cardiovascular and Pulmonary Rehabilitation: Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs. 6th EdVol. 28. Champaign, IL (USA): Reference & Research Book News; Human Kinetics, 2021.

77. Harwood AE, Russell S, Okwose NC, et al. A systematic review of rehabilitation in chronic heart failure: evaluating the reporting of exercise interventions. ESC Heart Fail 2021;8:3458-71.

78. Beckers PJ, Denollet J, Possemiers NM, et al. Maintaining physical fitness of patients with chronic heart failure: a randomized controlled trial. Eur J Cardiovasc Prev Rehabil 2010;17:660-7.

79. Mezzani A, Hamm LF, Jones AM, et al. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation, and the Canadian Association of Cardiac Rehabilitation. J Cardiopulm Rehabil Prev 2012;32:327-50.

80. Pelliccia A, Sharma S, Gati S, et al. 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease. Rev Esp Cardiol (Engl Ed) 2021;74:545.

81. Keltz RR, Hartley T, Huitema AA, et al. Do clinical exercise tests permit exercise threshold identification in patients referred to cardiac rehabilitation? Can J Cardiol 2023;39:1701-11.

82. Task Force of the Italian Working Group on Cardiac Rehabilitation and Prevention, Piepoli MF, Corrà U, et al. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction. Recommendations for performance and interpretation. Eur J Cardiovasc Prev Rehabil 2006;13:10-2.

83. Canadian Cardiovascular Society Heart Failure Management Primary Panel, Moe GW, Ezekowitz JA, et al. The 2013 Canadian Cardiovascular Society heart failure management guidelines update: focus on rehabilitation and exercise and surgical coronary revascularization. Can J Cardiol 2014;30:249-63.

84. Oliveira MF, Zanussi G, Sprovieri B, et al. Alternatives to aerobic exercise prescription in patients with chronic heart failure. Arq Bras Cardiol 2016;106:97-104.

85. Chaikijurajai T, Finet JE, Engelman T, et al. Prognostic value of hemodynamic gain index in patients with heart failure with reduced ejection fraction. JACC Heart Fail 2024;12:261-71.

86. Iellamo F, Manzi V, Caminiti G, et al. Validation of rate of perceived exertion-based exercise training in patients with heart failure: insights from autonomic nervous system adaptations. Int J Cardiol 2014;176:394-8.

87. Kim M, Kim MS, Lim SJ, Ahn JM, Kim JJ, Park SJ. Comparison of supervised hospital-based versus educated home-based exercise training in Korean heart failure patients. Korean Circ J 2017;47:742-51.

88. van der Meer S, Zwerink M, van Brussel M, et al. Effect of outpatient exercise training programmes in patients with chronic heart failure: a systematic review. Eur J Prev Cardiol 2012;19:795-803.

89. Karapolat H, Demir E, Bozkaya YT, et al. Comparison of hospital-based versus home-based exercise training in patients with heart failure: effects

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on functional capacity, quality of life, psychological symptoms, and hemodynamic parameters. Clin Res Cardiol 2009;98:635-42.

90. Moneghetti K, Carrik-Ranson G, Howden EJ, et al. Establishing the optimum use of high-intensity interval training in heart failure: current status and future directions. Curr Opin Physiol 2023;34:100669.

91. Gomes Neto M, Durães AR, Conceição LSR, et al. High intensity interval training versus moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: a systematic review and meta-analysis. Int J Cardiol 2018;261:134-41.

92. Haykowsky MJ, Timmons MP, Kruger C, et al. Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions. Am J Cardiol 2013;111:1466-9.

93. Iellamo F, Manzi V, Caminiti G, et al. Matched dose interval and continuous exercise training induce similar cardiorespiratory and metabolic adaptations in patients with heart failure. Int J Cardiol 2013;167:2561-5.

94. Dimopoulos S, Anastasiou-Nana M, Sakellariou D, et al. Effects of exercise rehabilitation program on heart rate recovery in patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil 2006;13:67-73.

95. Ellingsen Ø, Halle M, Conraads V, et al. High-intensity interval training in patients with heart failure with reduced ejection fraction. Circulation 2017;135:839-49.

96. Mandic S, Tymchak W, Kim D, et al. Effects of aerobic or aerobic and resistance training on cardiorespiratory and skeletal muscle function in heart failure: a randomized controlled pilot trial. Clin Rehabil 2009;23:207-16.

97. Pozehl B, Duncan K, Hertzog M, Norman JF. Heart failure exercise and training camp: effects of a multicomponent exercise training intervention in patients with heart failure. Heart Lung 2010;39(6 suppl):S1-13.

98. Laoutaris ID, Adamopoulos S, Manginas A, et al. Benefits of combined aerobic/resistance/inspiratory training in patients with chronic heart failure. A complete exercise model? A prospective randomised study. Int J Cardiol 2013;167:1967-72.

99. Beckers PJ, Denollet J, Possemiers NM, et al. Combined endurance-resistance training vs. endurance training in patients with chronic heart failure: a prospective randomized study. Eur Heart J 2008;29:1858-66.

100. Delagardelle C, Feiereisen P, Autier P, et al. Strength/endurance training versus endurance training in congestive heart failure. Med Sci Sports Exerc 2002;34:1868-72.

101. Feiereisen P, Delagardelle C, Vaillant M, Lasar Y, Beissel J. Is strength training the more efficient training modality in chronic heart failure? Med Sci Sports Exerc 2007;39:1910-7.

102. Tenenbaum A, Freimark D, Ahron E, et al. Long-term versus intermediate-term supervised exercise training in advanced heart failure: effects on exercise tolerance and mortality. Int J Cardiol 2006;113:364-70.

103. Stone JA, Arena R, Aggarwal S. Failing at heart failure therapies: are health behaviours to blame? Can J Cardiol 2017;33:1462-4.

104. Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: a review. JAMA 2023;329:827-38.

105. Bozkurt B, Fonarow GC, Goldberg LR, et al. Cardiac rehabilitation for patients with heart failure: JACC expert panel. J Am Coll Cardiol 2021;77:1454-69.

106. Tran M, Pesah E, Turk-Adawi K, et al. Cardiac rehabilitation availability and delivery in Canada: how does it compare with other high-income countries? Can J Cardiol 2018;34(10 suppl 2):S252-62.

107. Turk-Adawi K, Supervia M, Lopez-Jimenez F, et al. Cardiac rehabilitation availability and density around the globe. EclinicalMedicine 2019;13:31-45.

108. Kabboul NN, Tomlinson G, Francis TA, et al. Comparative effectiveness of the core components of cardiac rehabilitation on mortality and morbidity: a systematic review and network meta-analysis. J Clin Med 2018;7:514.

109. Shields GE, Wells A, Doherty P, et al. Cost-effectiveness of cardiac rehabilitation: a systematic review. Heart 2018;104:1403-10.

110. Sebastian SA, Padda I, Johal G. Supervised exercise training in heart failure with preserved ejection fraction: a systematic review and meta-analysis of randomized controlled trials. Curr Probl Cardiol 2024;49:102426.

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