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Exercise in Heart Failure—What Is the Optimal Dose to Improve Pathophysiology and Exercise Capacity?

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Abstract

Purpose of Review In this review, our aim is to summarize the evidence of exercise interventions in heart failure. Addressing pathophysiology, we discuss training modalities and optimal dose finding in exercising patients with reduced (HFrEF) and preserved ejection fraction (HFpEF).

Recent Findings While smaller studies showed a trend towards improved exercise capacity by high-intensity interval training in comparison with moderate continuous training in HFrEF, recent multicenter randomized trials were unable to confirm these findings. Considering the lack of effective drug therapies in HFpEF, exercise training plays an even more important role in this particular population.

Summary Exercise training in heart failure is beneficial in addition to medical and device therapy. Data are still mostly limited to HFrEF. Intensity should primarily be moderate at a daily base. The concept of "the higher the better" could not be confirmed for HFrEF. The overall concept of training is to maximally strain the periphery without straining the myocardium.

Keywords Heart failure · Heart failure with reduced ejection fraction · Heart failure with preserved ejection fraction · Exercise training · High-intensity interval training · Moderate continuous training

Introduction

Prevalence of heart failure (HF) is estimated to be 1–2% of populations in developed countries with an incidence rate of new diagnosis in 5–10 per 1000 persons per year [1]. Reduced exercise tolerance, shortness of breath, and peripheral edema are cardinal symptoms of HF, both in heart failure with reduced ejection fraction (HFrEF) and in heart failure with preserved ejection fraction (HFpEF) (Fig. 1). Etiological and epidemiological profiles differ in those two main disease entities: Patients with HFpEF are typically obese, prediabetic individuals with a higher prevalence in females and a history of hypertension and atrial fibrillation (AF), whereas patients with HFrEF often have a high cardiovascular risk and a history of coronary artery disease (CAD) and myocardial infarction [2, 3].

In addition to standard pharmacological HF therapy, leisure time physical activity and a structured HF exercise program are recommended in both groups of HF patients [4]. Recommendations are, however, only based on a limited number of randomized controlled trials primarily in HFrEF, but have also been extended to HFpEF. In this review, our aim is to critically appraise the current scientific evidence on exercise interventions in HF populations with either type of HF also addressing practical issues such as training modalities and finding the optimal exercise dose for individual patients with HFrEF and HFpEF.

History of Physical Activity and Myocardial Adaptation

Back in 1899, S.E. Henschen was the first to appreciate that regular endurance exercise has a physiological effect on the

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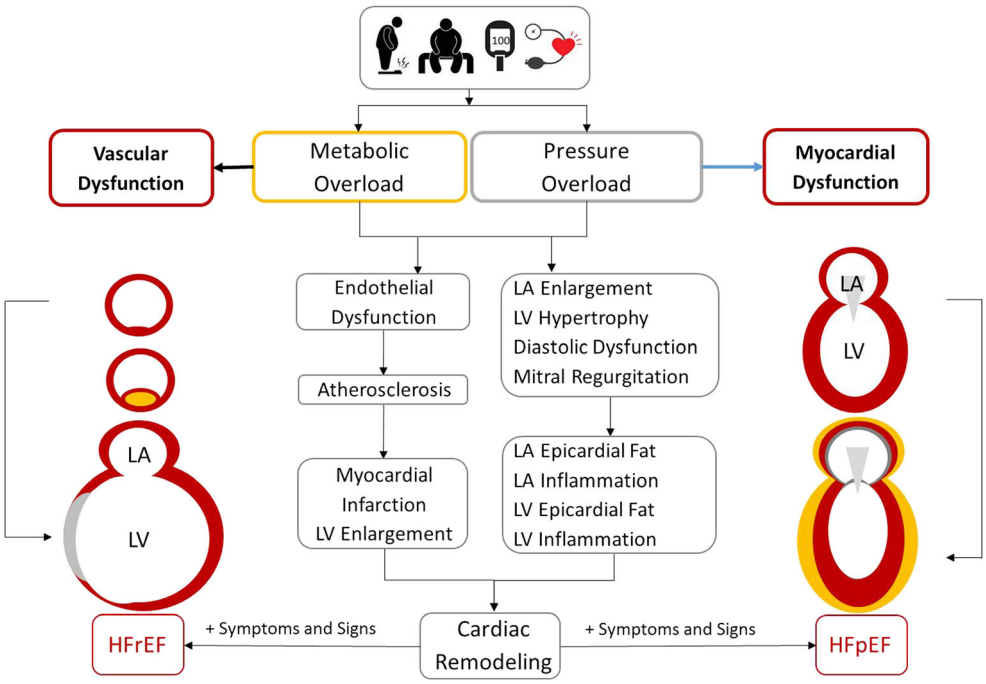

Fig. 1 Simplified pathophysiology in HFrEF and HFpEF. Obesity, inactivity, diabetes mellitus and hypertension lead to vascular and myocardial dysfunction and finally cardiac remodeling. HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LV, left ventricle

heart, revealed by an increment of its chamber sizes [5]. Half a century later in 1953, J. Morris published observations that, even beyond physiological effects in healthy individuals, exercise also had positive effects in preventing cardiovascular and myocardial diseases as evidenced by a lower incidence of CAD and mortality in physically more active London double-decker bus conductors compared with their more sedentary driver colleagues [6]. Moreover, he could confirm these preventative findings in other "physically active" jobs such as postmen compared with telephonists [6].

This knowledge, however, did not directly translate into the development of physical exercise as a treatment option for HF patients. Pharmacological treatment was even in the 1970s still very limited and mainly confined to digoxin and diuretics. Physicians were at this time reluctant to strain the dilated and malfunctioning left ventricle by exercise, and bed rest was seen as a viable treatment option in ischemic cardiomyopathy [7]. However, the experience of physical activity in cardiac rehabilitation after myocardial infarction and concomitant improvements of medical therapy in HF particularly by introduction of angiotensin-converting enzyme (ACE) inhibitors in the late 1980s rendered researchers more open to introduce physical activity also in HF patients. In 1988, Sullivan et al. introduced an exercise of moderate intensity in patients with left ventricular systolic dysfunction and observed improvements in objective measures of maximal exercise tolerance. A positive dose-dependent correlation between average exercise time per week and VO_2peak could be demonstrated. Interestingly, this early study demonstrated already that 30 min of exercise performed five times a week yielded the most beneficial effects [8].

Exercise in Heart Failure with Reduced Ejection Fraction

Driven by several smaller studies, which assessed the functional capacity of HF patients in the 1990s [9–11], a large, multicenter, prospective, randomized controlled study, the HF-ACTION trial, was initiated with the intention to clarify, whether exercise training (ET) would improve survival in a HFrEF population [12]. In this trial, 2331 patients were included with a left ventricular ejection fraction (LVEF) < 35% and NYHA grade II–IV. Training intensity was heart rate–guided: moderate continuous training (MCT), 60–70% of heart rate reserve (HRR). HRR is defined as the range between maximum (HRmax) and resting heart rate (HRrest) (HRR = HRmax − HRrest). The main finding was that regular ET in patients with HFrEF is safe and does not significantly increase cardiac events. After adjusting for HF etiology and four highly prognostic predictors (LVEF, history of AF, baseline exercise capacity, and depression score) continuous moderate ET was associated with a significant 11% reduction for both all-cause mortality or hospitalization and cardiovascular mortality or HF-hospitalization [12]. The HF-ACTION investigators had to deal with study limitations such as crossover between control and intervention group, but particularly, a very mediocre training adherence in the intervention group [12]. Despite

these limitations, the major scientific cardiological societies such as ESC (European Society of Cardiology) and AHA (American Heart Association) have since then defined exercise in stable HF patients as a class 1 and level of evidence A recommendation in their guidelines, when applied in addition to an optimized pharmacological therapy [4, 13].

Heart Failure with Preserved Ejection Fraction

Although symptoms and prognosis are similar in HFpEF and HFrEF patients, pathophysiology and the clinical therapeutic approach are different. While pharmacological treatments are well-established in HFrEF, the same strategies could not be convincingly proven to be effective in HFpEF. Several large trials, using established pharmacological strategies in HFrEF, such as ACE-inhibitors, angiotensin receptor blockers (ARB), or spironolactone, have failed to demonstrate substantial improvements in symptoms, morbidity, or mortality in patients with HFpEF [14–19]. So far, no pharmacological agent has shown to improve HF symptoms, exercise capacity, or prognosis in a HFpEF population. Nonetheless, risk factor treatment particularly focusing on blood pressure control is of primary importance.

As HFpEF is often associated with obesity and metabolic disturbances, exercise has also been addressed as a treatment modality in this HF entity. However, compared with HFrEF, current data on the effects of ET in HFpEF are still scarce [20]. In 2010, Kitzman et al. showed in 53 HFpEF patients that 16 weeks of ET could induce an improvement of VO_2peak [21]. The same group could confirm their previous findings in a larger group of elderly HFpEF patients also addressing the important role of weight reduction in obese individuals [22]. Prior to that study, Edelmann et al. [23] observed an improvement of diastolic function (E/e′, E/A) as well as left atrial volume in conjunction with improvements in maximal exercise capacity after 3 months of combined intervention of resistance and aerobic exercise training. Preliminary data in diabetic patients with diastolic dysfunction revealed superior effects on diastolic function by higher intensity interval than moderate intensity training [24]. However, data from larger randomized controlled trials on the role of exercise training and optimal intensity are lacking to date. Results from the Exercise in Diastolic Heart Failure trial (ExDHF) and OptimEx trial (Optimizing Exercise in HFpEF) are awaited in 2019 [25, 26].

Pathophysiology

Exercise has been shown to have numerous beneficial effects on different organ systems primarily triggered by stimulation of the musculoskeletal system during exercise. This inter-organ cross-talk between peripheral organs, e.g., peripheral muscle fibers, adipose tissue, hepatocytes, and cardiac muscle fibers, and the intra-organ cross-talk within the heart between epicardial fat tissue and myocardial tissue has emerged as a key phenomenon in understanding the effects of exercise on metabolism as well as vascular and myocardial function. Most details of cross-talk are by far not yet understood. According to the current state of knowledge, peripheral musculoskeletal adaptations trigger specific answers and feedback to the heart and other visceral organs also involving immune cells [27, 28]. In this section, we will focus on changes of the most important molecular mechanisms induced by ET.

Skeletal Muscle

The human body consists of a large amount of skeletal muscle (SM). In women, SM accounts for approximately 30%, in men for approximately 38% of total body mass [29]. Properly functioning muscles rely on a well-balanced equilibrium between anabolic and catabolic processes. Thus, degradation and synthesis of proteins are of special interest. Degradation is mainly regulated by ubiquitin-proteasome system (UPS), myostatin and autophagy [30•]. Autophagy was found to be upregulated in age-dependent denervation processes at the peripheral muscular level [31], also seen in patients with HF [32]. Myostatin is part of the transforming growth-factor hormones as a negative regulator of muscle mass. ET has led to a 36% reduction of myostatin mRNA and to a 23% decrease of myostatin itself after 12 weeks of ET [33]. Downregulation of substrates in the UPS was found after 4 weeks of exercise by Gielen et al. in HF patients [34]. On the other hand, anabolic factors—i.e., insulin-like growth factor 1 (IGF-1)—are significantly upregulated by exercise [35].

Energy supply in SM is mainly based on ATP synthesis in mitochondria. ET typically improves mitochondrial function [36] and increases neuronal nitric oxide synthase (nNOS), which itself regulates mitochondrial biogenesis [37]. Processes are not only regulated by nNOS in SM but in the myocardium as well [38].

Vasculature

Another isoform of nitric oxide (NO) synthase is the endothelial nitric oxide synthase (eNOS). eNOS is the main enzyme for NO production and regulated by vascular shear stress (VSS) by different pathways [39]. The clinical effects of ET on coronary endothelial function were first studied in patients with CAD by Hambrecht et al. [40]. A structured program of 4 weeks of continuous exercise training was effective in attenuating the paradoxical arterial vasoconstriction in epicardial conduit vessels by 54% and increased average peak flow velocity by 78%. Subsequently, the improvement in endothelial function by endurance exercise training was confirmed by several studies in patients with CAD [41–43] or diabetes [44]. With respect to the

molecular mechanisms responsible for the beneficial effect of exercise training on endothelial function, several mechanisms besides the modulation of eNOS have been discussed [30•].

Prevention of atherosclerosis is strongly related to effects of exercise-induced VSS which enhances vascular function by increasing the release of NO [45]. Improvement of endothelial function in HF, shown by Wisloff et al. [46], was not only dependent on ET itself, but also on intensity. Nevertheless, this association could not be confirmed by a substudy of the Study on Aerobic Interval Exercise Training in CAD (SAINTEX-CAD, Study on Aerobic INTerval EXercise training in CAD patients), comparing the impact of moderate continuous exercise training (MCT) with a high-intensity interval training (HIIT) protocol on endothelial function [47]. In this large multicenter study, both training regimens improved endothelial function without a difference between both training formats.

Myocardium

As mentioned above, over decades, physicians have been afraid of worsening cardiac function or inducing cardiac failure by exercise, especially in HF patients. Hambrecht et al. [10] were able to confirm data from the pilot data by Sullivan et al. [8] which showed that exercise was capable of improving LVEF by inducing a positive LV remodeling. These myocardial improvements are explained as secondary effects due to primary enhancement of endothelial function due to reductions in afterload [48, 49]. In addition to these secondary effects, primary effects have also been shown to be reflected by direct molecular changes within the myocardial muscle fibers. ET seems to attenuate cardiac fibrosis [50] and enhance myocardial function [30•]. Mechanisms are modulation of the anabolic/catabolic system: ET is able to reduce activation of UPS and myostatin in the myocardium in HF models [51, 52] as well as inducing activation of IGF-1 [53]. Further mechanisms are modulation of Ca^{2+}-handling [54] or even modulation of stem cell proliferation [55].

Breathing System

Respiratory muscle dysfunction is one of the reasons for dyspnea in HF patients [56]. Most data originate from HF models in animals, though [57, 58]. Nonetheless, in HFpEF models, ET has shown to prevent mitochondrial and functional impairments of the diaphragm compared with control groups, which developed fiber atrophy, fiber type shift, in situ mitochondrial respiration, and muscle weakness and increased fatigability [59].

Inflammatory Response

The different facets of an anti-inflammatory response to ET are complex and not fully understood. Best understood mechanisms are alterations in expression of interleukin (IL)-6 and tumor-necrosis-factor alpha [60]. Anti-inflammatory counteractors include IL-1, IL-10, IL-11, and IL-13 receptor antagonists [61]. In healthy subjects, their role is to keep a balanced system, whereas in HF patients, this system is imbalanced and depends on disease severity [62].

Future and Perspectives

Micro-ribonucleic acid (miRNA) are non-coding RNAs, which regulate gene and protein expression [63]. Exercise has proven to regulate miRNAs. In humans, miR-1, miR-133a, miR-133b, and miR-206 have been shown to respond to ET, but their role in regulating SM adaptation is still unclear. MiRNAs are not only involved in SM, but also in the heart [64], endothelium [65], and other organ systems. MiRNA may play an important—not yet completely understood—role in ET, but this recently discovered field is complex and data in HF populations are still lacking.

In summary, exercise induces a global and specific stress response of the whole body organ system. Effects are regulated and adaptations tuned on different molecular levels and in most—if not all—organ systems. The crux of the matter in ET is on the one hand its complexity in targeting multiple entities like metabolism and function at the same time. On the other hand, ET consists of repetitive bouts of stress and stress response in alteration with recovery periods—compared with chronic stress, which is not balanced by stress and recovery periods.

Optimal Dose of Exercise: High-Intensity Interval Training or Moderate Continuous Training?

Epidemiological data have shown that regular exercise (30 min of daily moderate walking) leads to a 16% decrease in cardiovascular and all-cause mortality, and mortality can even be decreased by almost 40% when performing at higher intensities [66]. This finding has been confirmed in several large epidemiological studies around the world like the Prospective Urban Rural Epidemiology (PURE) study [67] or the Copenhagen City Heart Study [68]. This has been explained by higher strain on molecular mechanisms, peripheral as well as central, and superior metabolic functional as well as clinical effect with higher intensity exercise than moderate level [69]. However, transferral of this concept to cardiac patients particularly with HF has been challenging [70].

The HF-ACTION study evaluated primarily moderate exercise intensity [12], but subanalyses revealed that intensity was higher in some individuals, and that these individuals improved more regarding maximal exercise capacity than others training at lower intensity levels [71]. In addition, a few smaller studies demonstrated superior beneficial cardiovascular effects by

high-intensity interval training (HIIT) than by MCT. Wisloff et al. [46] pointed out the most impressive difference between those two groups, measuring VO_2peak as an indicator of training success in HF patients [46]. VO_2peak improved significantly ($p < 0.001$) after 12 weeks of supervised training by 6 ml/min/kg (standard deviation (SD) 2.1 ml/min/kg) compared with VO_2peak gain of 1.9 ml/min/kg (SD 0.9 ml/min/kg) in the MCT group. However, this study was conducted with a small numbers of HF participants ($n = 17$) only. The same study protocol was therefore followed in a larger trial, the Study of Myocardial Recovery After Exercise Training in Heart Failure (SMART-EX) [72•] involving $n = 261$ HF patients also comparing HIIT vs. MCT vs. recommendation of regular exercise (RRE). However, in contrast to the pilot study, the effects of HIIT were significantly less than expected from the smaller trial. Reasons for these differences have been attributed to age and physical fitness differences between the studies. Patients in the latter study were on average 15 years younger and had a higher VO_2peak at baseline. However, the most important limitation has been training intensity. Patients in HIIT trained on average < 90% than the expected 90–95% of HRmax and patients in MCT trained at a higher intensity level of around 80% rather than the expected 60–70% of HRmax. This might have reduced the difference between the intervention groups. Nonetheless, data have overall revealed that clinically moderate exercise intensity seems to be sufficient for improvement of exercise capacity [73]. However, training intensities below 60% of HRmax seem to be too low to induce significant effects.

Devices

Implantable Cardioverter-Defibrillator

The largest evidence is based on a subanalysis [74] of the HF-ACTION study [12], in which 1053 patients (45%) had an ICD implanted at baseline with a mean LVEF of 24%. Five hundred forty-six patients were randomized to the exercise group (MCT) vs. 507 to the control group. After a median follow-up time of 2.2 years, 108 (20%) in the MCT group and 113 (22%) in the control group had a shock from ICD; however, this difference was not statistically significant. Previous ventricular fibrillation/tachycardia VF/VT as well as AF/atrial flutter were predictors for shocks. Importantly, ET was not associated with shocks. Therefore, exercise training is feasible in HFrEF patients with ICDs, provided patients are under optimal pharmacological therapy, and HF has been stable for at least 4–6 weeks (ideally 3 months). Furthermore, maximum CPET should be performed before starting the training, and the ICD settings need to be adjusted to maximal heart rate under maximal medication.

Left Ventricular Assist Devices

Most commonly implanted devices are assisting the left ventricular (LVADs) which are used as a bridge to transplantation as well as destination therapy in end-stage HF. Due to improvements of the systems over the last decade and mismatch of donor organs, the patient population with LVADs is constantly increasing [75]. Also, in these patients, ET on top of standard-of-care treatment seems to have additional benefits regarding VO_2peak and quality of life after maximal intervention of 18 weeks [76]. These data arise from four small randomized controlled trials. Multicenter studies have not been published so far, but are under way (NCT03369938).

Training Recommendations

ET should not be seen as an alternative to established HF treatment, consisting of pharmacological and device therapy, but should be seen as complementary to established HF treatment measures in stable patients.

Prerequisite for introducing exercise is a thorough medical examination (history, physical examination, echocardiography, and stress test). We recommend cardiopulmonary exercise testing (CPET) for stress testing. In addition to a usual stress test, pulmonary function parameters (O_2 diffusion capacity by assessing pO_2) as well as prognostic parameters should be assessed. Thereby, potential alternative or contributing reasons for dyspnea can be identified, and submaximal as well as maximal exercise capacity (in terms of watts and VO_2peak) can be determined. The CPET is ideal for prescribing exercise intensity via first (VT1) and second ventilatory thresholds (VT2) [77].

Mode of Training

Although endurance training is clearly the basis in HF exercise programs, this training should ideally be combined with resistance training (RT) (Table 1). RT positively influences proprioception leading to better stability and coordination. Muscle strengthening is a successful approach in preventing loss of muscle mass and strength in HF. The combination of endurance and RT optimally strains the periphery also improving the cardiopulmonary capacity and pathophysiology [78].

We propose supervision and guidance of training sessions by educated medical persons—physician, physiotherapist, or sports scientist be based on local practice. However, professional back up by a physician is strongly advised, especially within the first weeks to months of training. During this phase, though, training intensity should be gradually increased and medication adapted. Furthermore, self-monitoring is an important skill which should be acquired during the initial

Table 1 Recommendations for structured exercise training in chronic heart failure

Training progress	Week	Target	MCT	Modified HIIT	Resistance
Beginning: start low, go slow	wk 1-2	Frequency	2-3x / wk, optimally split in 2 sessions per day		2x / wk
		Time	Aim at 15min persisting workload: Symptom and comorbidity guided increase		15 repetitions, 1-2 circuits
		Intensity	40-50% VO_2peak		<30% 1-RM
Progression: when beginning was well tolerated	wk 3-4	Frequency	Increase frequency up to 3-4x / wk		Increase repetitions (15-20)
	wk 5-7	Time	Increase sessions duration to 15–20 min, finally up to 30-45 min	Alternation of short intervals of higher intensity exercise workload (10s, 50-70% VO_2peak) and longer recovery period (3 min, 40% VO_2peak). Increase duration to 15-20 min, finally up to 30-45 min	Increase circuits (2-3)
	wk 8-12	Intensity	Increase intensity (50 to 60%, 60 to 70% of VO_2peak)	Increase duration of intervals (up to 2 min) and decrease recovery periods (down to 2-3 min)	Increase intensity (30-50% 1-RM)
Maintenance: when progression was well tolerated	>12 wk	Goals	60-70% VO_2peak	Interval intensity 70-80% VO_2peak. Recovery period 50% VO_2 peak.	15-20 repetitions, 40-60% 1-RM

MCT, moderate continuous training; *HIIT*, high-intensity interval training; *wk*, week; *mt*, month; *1-RM*, one repetition maximum

training phase and prompt adequate reaction on symptoms and HR abnormalities.

Guiding

Intensity can be guided by several modalities: rate of perceived exertion Borg (RPE), percentage of HRmax, percentage of HRR, or ventilatory thresholds (VT1 and VT2). Optimal individual guidance is achieved by VT, but percentage of HRmax or percentage of HRR are favored by most clinicians not familiar with the CPET data. In these recommendations, data, e.g., on onset of arrhythmias in HFrEF during exercise or exaggerated blood pressure response in HFpEF, should be included.

Start Low–Go Slow

At the very beginning, motivation is essential. Primary goal is to integrate physical activity into daily life, starting with small periods of 5 to 10 min daily. Fitness trackers or pedometer may be helpful for motivation and self-monitoring. Duration should be increased slowly by 1 min per session per week leading to 20-min sessions daily after 2–3 months.

Intensity

Moderate exercise intensity should be pursued and performed without clinical problems before intensity can be increased once or twice weekly. A valuable option consists of implementing intervals in the meaning of alternating intensity. While starting with ET, intensive intervals should last no longer than 1 min, alternating with moderate intensity in between. When well-tolerated, a progression with intervals up to 2 min or even longer periods can be achieved. In general, a maximal intensity of 80% of HRR alternating with 60–70% HRR can be recommended (2 min higher and 4 min moderate intensity, 4 times repetition added by 5 min warm-up and 5 min cool-down). This intensity equals the alternating intensity between VT1 and VT2. This ventilator parameters have to be correlated to HR values for easy monitoring. Therefore, in most patients, moderate regular training intensity should be applied for the first 3 months. Higher intensity may be introduced following this period. Very high training intensity should be limited to long-term stable subjects. If a variety in training is desired by the patient, HIIT can be altered with MCT on an individual base as none of these modalities has shown superiority in HFrEF. Intervals of 4 min seem too long in this particular population. Shorter intervals of 1–2 min may be favorable in order to achieve sufficient intensity.

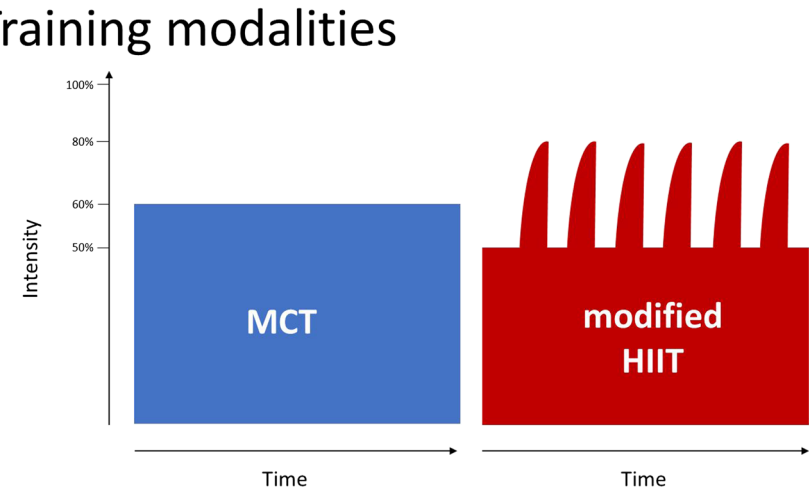

Fig. 2 Training modalities: MCT and modified HIIT. MCT, moderate continuous training; HIIT, high-intensity interval training

Intensity adjustment over time is important, as rate of perceived exertion (RPE) of 11–14 ("light"–"somewhat hard"; Borg Scale ranges from RPE 6–20) should be achieved for optimal training effects.

As discussed in the previous sections, training modality in HFpEF is still unclear. Until larger trial data are available, the abovementioned training recommendations are also valid in HFpEF (a summary of training recommendations and modalities is presented in Table 1 and Fig. 2). In these patients, a steeper increase in duration and frequency can be pursued.

Training Frequency

In general, the minimum frequency of training is 3 session per week. These sessions should aim at 20–40 min, but shorter duration or halving them for a morning and evening session is possible. In deconditioned, handicapped patients, training duration but not frequency can be lowered starting with fragmented duration of 5–10 min, gradually increasing time and later intensity.

Special Conditions

Patients with implanted ICD should always start training under supervision. Target heart rate is typically 20 beats per minute lower than VF/VT detection rate. Intensity guiding in atrial fibrillation and LVAD patients is consequently not achieved by HR but rather by RPE (Borg Scale).

Conclusion

Exercise training in heart failure is beneficial in addition to medical and device therapy. Data are still mostly limited to HFrEF. Intensity should primarily be moderate and frequency optimally daily. The concept of "the higher the better" could not be confirmed for HFrEF. It will have to be seen whether this is different to HFpEF. The overall concept of training is to maximally strain the periphery without straining the myocardium.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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