Physical Training in Heart Failure with Preserved Ejection Fraction

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Heart failure (HF) is a clinical syndrome caused by functional and/or structural cardiac abnormalities in association with elevated natriuretic peptides or other objective evidence of pulmonary and/or systemic congestion.[1] These abnormalities result in increased intracardiac pressures and/or inadequate cardiac output at rest and/or during exertion.[2]

HF with preserved ejection fraction (HFpEF), although it is included in this definition, is a pathology with a more challenging and complex approach, and it is more common in older patients, predominantly in the female sex, as well as in patients who have multiple comorbidities such as atrial fibrillation, chronic kidney disease, and other non-cardiovascular pathologies, which sometimes overlap with the patients' clinical condition.[2] According to more recent data, 50% of patients with HF have preserved ejection fraction, and its prevalence in relation to HF with reduced ejection fraction (HFrEF) continues to ascend at an annual rate of approximately 1%.[3]

Diagnosis is still considered a challenge, and it involves the evaluation of various clinical, echocardiographic, and functional factors. The use of scores, such as the H2FPEF and the HFA-PEFF, is recommended to improve the accuracy of the process, and invasive hemodynamic measures may even be used in cases specific.[2,4]

Few randomized clinical trials have shown positive outcomes, analyzing combined or secondary outcomes, mainly the reduction of hospitalizations due to HF, or they have shown benefits in subgroup analyses.[5-8] This characteristic reinforces the current concept of the presence of different phenotypes within the syndrome, which could then benefit from individualized approaches and therapies.[3]

Consequently, in this scenario, non-pharmacological treatment has become an essential first-line approach to strengthen therapy in order to promote improved survival and quality of life.

Evidence has shown that cardiopulmonary rehabilitation in HFpEF, based on aerobic exercise, promotes cardiovascular protection with multisystem benefits, such as inhibition of cardiomyocyte hypertrophy; reduced inflammation, fibrosis, and microvascular dysfunction; and improvement in mitochondrial metabolism and endothelial function. Randomized controlled studies have found varying results regarding the effects of exercise in this population, whereas other studies have shown an increase in cardiorespiratory fitness, exercise tolerance, and quality of life, as well as improved diastolic function.[9] The objective of this review is to understand the rationale for the beneficial mechanisms of exercise in HFpEF, review the main scientific data that support this measure as part of the non-pharmacological treatment of this pathology, and describe how and why we should encourage our patients to adopt the practice of physical exercises in their daily lives.

Pathophysiological rationale for the benefits of physical training in HFpEF

When we compare patients with HFpEF to a control group of patients with hypertension or other comorbidities, we see that the former's peak oxygen consumption (VO_2) is 30% to 70% lower than that of the other groups, as shown in Figure 1.[10]

Reduced VO_2 is a parameter of reduced aerobic functional capacity, which is currently considered a new vital sign, as well as a marker of independence for daily activities, which increases the chance of functional dependence.[11] Several mechanisms seem to explain this fact in patients with HFpEF. An initial study by Kitzman et al hypothesized that the following 3 mechanisms are involved in this reduction in functional capacity: a reduction in cardiac output on exertion, a rapid increase in pulmonary capillary pressure, and a smaller difference in the arterial-venous oxygen gradient,[12,13] with several subsequent studies diverging as to which pathophysiological mechanism would be predominant in HFpEF. It is especially interesting that the reduction in the arterial-venous oxygen gradient possibly occurs due to hypoperfusion of peripheral skeletal muscles[14] or to a decrease in skeletal muscle oxidative metabolism.[15] Both mechanisms reinforce the hypothesis of "peripheral hearts", which will be subsequently discussed. Another mechanism that seems to explain exercise intolerance in this group of patients is chronotropic incompetence,[16] which is particularly important in patients with specific etiologies of HFpEF, such as cardiac amyloidosis.

Keywords

Physical training; Heart Failure; Preserved Ejection Fraction; Cardiac Rehabilitation

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Manuscript received September 13/09/2022, revised manuscript September 24, 2022, accepted September 24, 2022

DOI: https://doi.org/10.36660/abchf.20220064

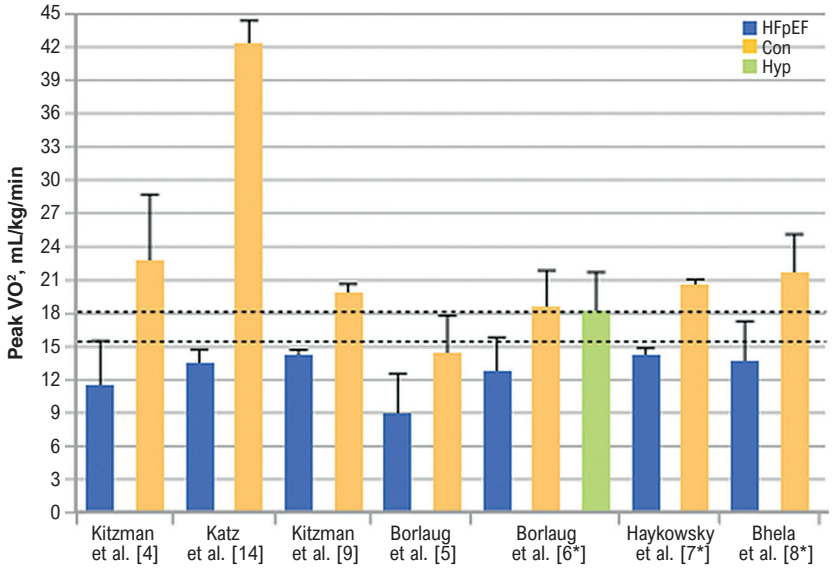

Figure 1 – *Comparison of aerobic capacity between patients with heart failure with preserved ejection fraction; patients from a control group matched by age, sex, and other comorbidities without heart failure; and patients with hypertension without heart failure. Adapted from Haykowsky, M et al.[10] HFpEF: heart failure with preserved ejection fraction; Hyp: hypertension; VO²: oxygen consumption.*

Clinical studies involving exercise or cardiovascular rehabilitation and HFpEF

In spite of similar prevalence between HFpEF and HFrEF, there are considerably fewer data on the role of physical training in HFpEF. Nonetheless, 7 controlled trials (5 randomized, 1 multicenter) on exercise training in patients with HFpEF have demonstrated that physical training is a safe and effective intervention to improve symptoms, increase aerobic capacity and endurance, and improve self-reported quality of life.[17-24] We will describe some of these studies in the following paragraphs.

In HFrEF, it is known that physical training improves exercise capacity and reduces morbidity.[25] As suggested by previous meta-analyses, Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) showed that an exercise training program prescribed in patients with chronic symptomatic HFrEF was safe, with a modest reduction in clinical events when added to optimal medical therapy.[26,27]

In 2007, a prospective, multicenter study on physical training in HFpEF was conducted to investigate whether exercise training would improve exercise performance, diastolic function, and quality of life in patients with HFpEF over 3 months. The results showed that the mean increase in peak VO_2 was 2.6 ml/min/kg in the physical training group compared to a slight decrease of 0.7 ml/min/kg in the control group. The net benefit of training was 3.3 ml/min/kg (95% confidence interval: 1.8 to 4.8, p = 0.001), translating to a number needed to treat of 3.5 (95% confidence interval: 2.0 to 12.0, p = 0.006) to achieve an increase of at least 3 ml/min/kg at the individual level. Diastolic function in exercise with an increase in peak VO_2 was correlated with improved E/e' ratio (r = −0.37, p = 0.002), thus improving diastolic function and quality of life in patients with HFpEF.[21]

Another 2:1 randomized, prospective study, carried out in Israel, selected patients with HF with preserved, mildly reduced, and reduced ejections fractions to practice guided physical activity, with the control group receiving only routine treatment without guidance regarding physical exercise. Their results showed an improvement in ejection fraction (p = 0.02), and there was an improvement in exercise tolerance in the group of patients with HFpEF.[22]

A systematic review of exercise-based rehabilitation among patients with HF regardless of ejection fraction evaluated outcomes such as all-cause mortality, all-cause hospitalizations, and quality of life. The study suggests that there is a reduction in mortality only after 12 months of follow-up (RR 0.88, 95% confidence interval 0.75 to 1.2), in addition to a reduction in all-cause hospitalizations (RR 0.70, interval of 95% confidence interval 0.60 to 0.83) and hospitalizations due to HF in fewer than 12 months (RR 0.59, 95% confidence interval 0.42 to 0.84). It also suggests improved quality of life according to the Minnesota Living with Heart Failure Questionnaire (mean difference −7.11, 95% confidence interval −10.49 to −3.73). Unfortunately, this publication did not analyze HFrEF and HFpEF populations separately.[28]

Another publication of a Portuguese cross-sectional study, which was specific to the population with HFpEF, provided evidence of a direct relationship between quality of life and physical fitness, which was evaluated according to the following 3 parameters: cardiorespiratory fitness, dynamic balance, and mobility and muscular fitness. The parameter

of dynamic balance and mobility was shown to be the only predictor independently associated with the quality of life score according to the Minnesota Living with Heart Failure Questionnaire in the physical (beta 0.570, p = 0.04) and emotional (beta 0.611 p = 0.002) dimensions, making it possible to infer the importance of including this group of exercises in these patients' rehabilitation.[29]

Notwithstanding proof of positive outcomes in patients with HF, an Italian study showed that a rehabilitation program with moderate intensity exercises for patients with HF, regardless of ejection fraction, during the first 4 months, did not show a significant change in ejection fraction (HFpEF: 54.61% ± 3.31% versus 54.21% ± 2.32% and HFrEF: 36.56% ± 2.31% versus 39.59% ± 2.95%; p group = 0.0001, p time = 0.57, p interaction = 0.46), left ventricular systolic diameter (HFpEF: 36.22 ± 1.57 versus 40.93 ± 4.15 and HFrEF: 51.67 ± 2.84 versus 51.90 ± 3.19 mm; p group = 0.004, p time = 0.19, p interaction = 0.24), left ventricular systolic diameter (HFpEF: 55.00 ± 1.58 versus 50.78 ± 1.93 and HFrEF: 65.33 ± 2.80 versus 65.49 ± 3.44 mm; p group = 0.002, p time = 0.12, p interaction = 0.10), or global longitudinal strain analysis (HFpEF: −13.73 % ± 1.23% versus −12.74% ± 0.95% and HFrEF: −9.59% ± 0.94% versus −9.77% ± 0.98%; p group = 0.0001, p time = 0.57, p interaction = 0.46).[30]

A very interesting subanalysis of physical activity in patients with HFpEF came from the TOPCAT trial. Some interesting points are raised in this article. First, only 11% of the 1751 patients followed the physical activity recommendations given by the guidelines at the time, which shows the poor adherence (by patients or by physicians themselves) to physical activity in this group of patients. Second, when comparing patients with a worse degree of physical activity with those with levels close to ideal, there was an increase in hospitalization due to HF and mortality in the first group. Finally, there was a dose-response relationship, where only physical activity levels above those recommended by the guidelines were related to a lower risk of hospitalization and mortality (Figure 2).[31]

When evaluating the types of physical training in HFpEF, there is evidence showing that intervals of high-intensity exercises seem to present better peak VO_2 and improved diastolic ventricular diameter compared to moderate-intensity training,[30] making it possible to infer that there is an exercise profile with better results in this population.

How to practice or prescribe physical exercise in HFpEF?

In the mid-1980s, Weber demonstrated the clinical applicability of the cardiopulmonary exercise test (CPET) through the use of peak VO_2 in classification of HF.[32] In 1991, Mancini stratified the risk of cardiovascular death using peak VO_2 values in patients with advanced HF.[33] Since these 2 studies, but mainly after the 2000s, with the discovery and use of new variables, the method has been gaining ground in therapeutic and prognostic evaluation and in the prescription of exercise for patients with HFrEF.[34] Over the past 10 years, with the advance of pathophysiological knowledge of HFpEF, the method has also been used in the evaluation of exercise intolerance and in the prescription of physical rehabilitation in patients with preserved systolic function.[16]

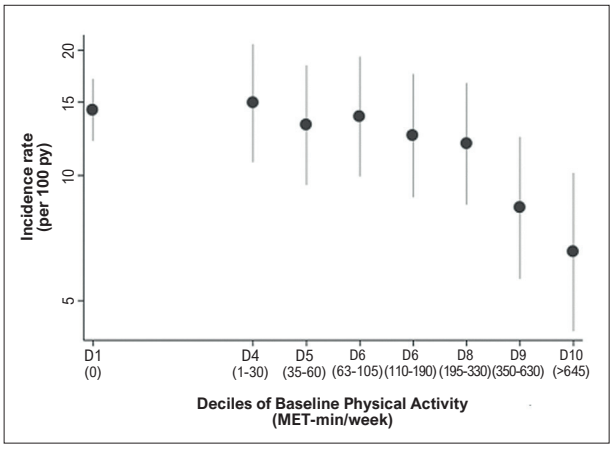

Figure 2 – *Incidence rates of the primary endpoint (cardiovascular death, resuscitated cardiac arrest, or hospitalization due to heart failure) in patients from the TOPCAT trial, according to baseline physical activity level. Adapted from Hegde et al.[31]*

The CPET allows for objective and quantitative evaluation of functional capacity through the measurement of VO_2 at peak effort. In the context of exercise prescription, the intensity of aerobic training can be calculated using the heart rate (HR) reserve, or preferably, the HR corresponding to determined percentages of peak VO_2.[35,36] In patients with HFpEF, continuous aerobic exercise is recommended for 45 to 60 minutes, 3 to 5 times a week, at moderate to high intensity. During the first few weeks of exercise, training HR should correspond to 40% to 50% of peak VO_2. During the following weeks, training HR should be gradually increased to 70% to 80% of peak VO_2. Alternatively, a percentage of HR reserve can be used as a measure of training intensity. HR reserve is the value of the difference between the peak HR obtained on the conventional exercise stress test and the baseline resting HR (peak HR − resting HR), and it corresponds to the increase in HR obtained at the maximum effort achieved. For exercise prescription, the HR range for beginning training is calculated as follows: 40% to 70% (peak HR − Resting HR) + resting HR.[36] For instance, if a patient has a resting HR of 70 bpm and they reached a peak HR of 160 bpm, they have a HR reserve of 90 bpm. Thus:

Training HR lower limit:
$0.4 \times 90 + 70 = 36 + 70 = 106$ bpm

Training HR upper limit:
$0.7 \times 90 + 70 = 63 + 70 = 133$ bpm

Training range (initial): from 106 to 133 bpm

Progressively, the training range should be increased during the rehabilitation process.

Several studies have demonstrated the efficacy and safety of high-intensity interval training (HIIT) in patients with HFpEF.

This type of training appears to improve cardiac autonomic function, through baroreflex modulation, reduced arterial stiffness, and mediation of vagal control resulting from reduced circulating angiotensin II. HIIT is based on the repetition of short to long activities of high-intensity exercises interspersed with periods of active or passive recovery (15 to 60 seconds of exercise at HR at 80% to 100% of peak VO_2, followed by 15 to 60 seconds of exercise at 40% to 60% of VO_2 peak, for example). Patients with HFpEF should start training at short intervals and gradually increase the exercise time.[37] The Borg scale of perceived exertion can also be used to guide the progression of training, regardless of whether the modality is continuous or interval. A brief period (3 to 5 minutes) of warm-up and cool-down should be recommended before and after each training session.[16]

Physical training programs should involve not only aerobic exercises, but also stretching, strength, and breathing exercises. In 1984, Rigatto et al, in a study on cardiovascular physiology, defended the idea of "peripheral hearts" affirming that the circulatory pump function was not exclusive to the heart and that other organs also act as sources for the transportation of blood and uptake of oxygen by the body. Strengthening the "pulmonary heart" by training the intercostal and diaphragmatic muscles improves respiratory mechanics, increases blood flow, and relieves the sensation of dyspnea.[38] Strength exercises should be prescribed 2 to 3 times a week with a load defined by percentages of "maximum resistance" (MR). MR corresponds to the greatest absolute weight that a patient can support when exercising a certain muscle group. This training should be prescribed at low intensity with higher number of repetitions (30% to 40% of RM, 10 to 15 repetitions) or at higher intensity with lower number of repetitions (40% to 60% of RM, 8 to 12 repetitions). For instance, a patient who has a MR of 3 kg for biceps flexion should start strength training with a load of 1.2 kg (40% of 3 kg). Progressively, the load and the number of repetitions should be increased under the supervision of a physical therapy or physical education professional. With the increase in muscle mass, there is an increase in peripheral oxygen uptake (with an increase in the arterial-venous oxygen gradient) and a consequent increase in the peak VO_2 value, as reflected by the improvement in functional capacity.[16]

Conclusion

HFpEF is a clinical syndrome, which, like HFrEF, leads to an accentuated exercise limitation. Therapeutic approaches are still limited, and they remain unsatisfactory, to the extent that they do not modify the natural course of the disease. As a non-pharmacological intervention, physical training has emerged as a potential strategy to be included in the therapeutic arsenal of HFpEF.

Cardiac rehabilitation causes exercise capacity to increase and clinical symptoms to improve.[39] Physical training is a fundamental component of these programs, in conjunction with dietary guidelines, encouraging adherence to medication, preventive measures such as vaccination, abstinence from alcohol and tobacco, and medical consultations. Prescriptions should ideally be individualized, taking into consideration the combination of moderate- and/or high-intensity aerobic training, localized muscular resistance exercises, and respiratory muscle training (ventilatory training).

Unfortunately, the data related to hard outcomes, such as mortality, are still not conclusive enough for us to be able to affirm that cardiovascular rehabilitation has any impact on them. Nevertheless, the improvement in these patients' peak VO_2, functional capacity, and independence for activities of daily living, in addition to the fact that it assists in controlling the multiple comorbidities that normally accompany these patients with HFpEF, lead us to conclude that physical training plays an important part in their treatment.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for important intellectual content: Montenegro CEL; Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Aguiar MIR, Tavares DCF, Nogueira FF, Lyra ACAS, Gomes TQM, Montenegro CEL.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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