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REVIEW ARTICLE

Monitoring the Effects of Cardiac Rehabilitation Programs in Heart Failure Patients: The Role of Biomarkers

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Abstract

Heart failure (HF) is characterized by poor exercise tolerance and reduced ability to perform routine daily activities. Cardiac rehabilitation (CR), which includes exercise training, has shown a role in improving cardiac remodeling, functional capacity and HF outcomes as a consequence of its beneficial effects on neurohormonal dysfunction, endothelial function, vascular tone and peripheral oxygen extraction. Although a multiparametric evaluation, including physical examination, blood sampling, echocardiographic and cardiopulmonary exercise testing parameters, is routinely performed during CR programs, the use of cardiac biomarkers, in particular natriuretic peptides (NPs), is still poorly adopted and characterized. In this article we analyze the potential role of biomarkers in monitoring the success of rehabilitation programs and the potential implications of their use in clinical practice. Indeed, NPs measurements might represent an important tool to modulate the rehabilitative interventions with a favorable cost-effectiveness profile.

Keywords Cardiac rehabilitation · Natriuretic peptides · Cardiac biomarkers · Heart failure

1 Introduction

Heart failure (HF) is generally characterized by poor exercise tolerance and often by inability to perform routine daily activities [1]. These clinical manifestations are the consequence of multiple detrimental pathophysiological mechanisms including inadequate cardiac output, left ventricular diastolic dysfunction with high filling pressures, neurohormonal dysregulation, sodium and water retention, endothelial and mitochondrial dysfunction, impaired peripheral oxygen extraction and alterations in fiber composition at muscle level, a less than normal decrease in dead space-to-tidal volume ratio and impairment of pulmonary perfusion [1–5].

In addition, HF patients present a reduced vasodilator capacity during exercise, due to a decreased release of endothelium-derived relaxing factors such as nitric oxide and an exaggerated vasoconstrictive response associated to increased levels of norepinephrine, angiotensin II, endothelin and vasopressin. These processes lead to peripheral hypoperfusion with a subnormal blood flow adaptive response, resulting in early anaerobic metabolism and development of fatigue during physical activity [1–6].

Independent from left ventricular ejection fraction (LVEF) level, exercise intolerance is associated with poor quality of life (QoL) and with a worse prognosis in patients with HF, as related to an increased risk of hospitalizations and cardiovascular mortality [7, 8].

Cardiac rehabilitation (CR), consisting in multidisciplinary programs which include exercise training (ET), psychosocial assessment, lifestyle modifications and education about adherence to treatment, has gained an increasing role in the management of HF in acute, convalescent and maintenance phases [8–11].

Aerobic exercise or endurance training, which includes treadmill walking, swimming, dancing, cycling, represents the milestone of ET in HF particularly with an approach

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based on moderate continuous training which is safe and well-tolerated. Recent studies have shown that the addition of dynamic resistance exercises in a combined training strategy may further improve muscle strength and endurance without adverse events and that high-intensity intermittent exercise may also have benefits on functional capacity [12–15]. ET has been demonstrated to play an important role in improving neurohormonal dysfunction, endothelial and skeletal muscle function and in reducing peripheral vascular tone [12–15].

In spite of general consensus recognizing the key role of cardiac rehabilitation in HF, there are wide areas of improvement especially in assessing and monitoring the effects of cardiopulmonary rehabilitation in HF. In this view, multiparametric assessment of the clinical course of the rehabilitative intervention may bring significant gain (Fig. 1).

In this article we will discuss the available evidence about the effects of CR on cardiac remodeling, functional capacity and HF outcomes, the potential role of biomarkers in monitoring the success of the rehabilitation program and the potential implications of their use in clinical practice.

2 Effects of Cardiac Rehabilitation on Cardiac Remodeling

The impact of cardiac rehabilitation of left ventricular structure and function is of paramount importance, given the clinical benefits that may be related to an improved ventricular function.

Preclinical studies have shown that aerobic training may enhance cardiomyocyte fractional shortening, contraction rate, relaxation rate and maximal power output by up to 50%, 20%, 40%, and 60%, respectively [16]. Moreover, ET increases myofilament calcium (Ca2þ) sensitivity and flux in the cardiomyocytes as a consequence of improved coupling of L-type Ca2þ channels and ryanodine receptors, increased SERCA2a and sodium-calcium exchanger expression and activity [17].

In HF patients with an ischemic etiology Port and colleagues demonstrated that ET was able to significantly increase LVEF starting from a baseline level < 25%, with a positive trend in patients with higher LVEF, though statistical significance was not achieved [18]. Consistently, Hollriegel and colleagues showed that LVEF increased from 24 to 38% after 12-month CR, with an associated continuous

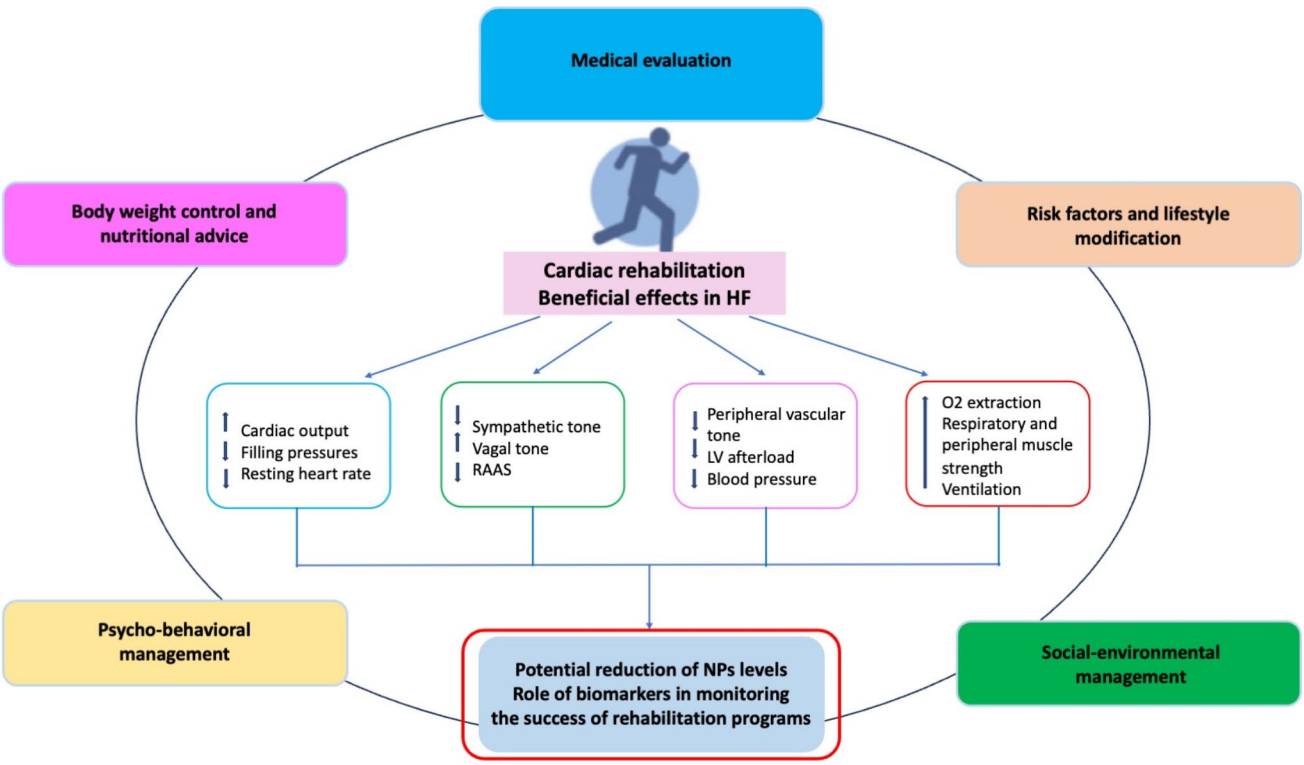

Fig. 1 Benefits of cardiac rehabilitation in heart failure: a multiparametric approach. Cardiac rehabilitation consists in multidisciplinary programs involving medical evaluation, lifestyle modification, control of risk factors and body weight, nutrition advice, social-environmental and psycho-behavioral management. In patients with heart failure cardiac rehabilitation exerts different beneficial effects, that may produce a reduction of cardiac biomarkers and in particular of natriuretic peptides. In such a context, biomarkers may play an important role in monitoring the success of rehabilitation programs as part of a multiparametric approach. HF, heart failure; LV, left ventricle; NPs, natriuretic peptides

decrease in LV end-diastolic diameter from baseline at 3, 6, and 12 months of ET [19]. Similar results were reported by Besnier and colleagues who demonstrated that high-intensity interval training produced a significant LVEF increase from 36 to 39% and a concomitant decrease of LV end-systolic volume [20]. In addition, CR has been shown to reduce LV end-diastolic pressure, to enhance nitric oxide production and to increase plasma levels of vascular endothelial growth factor (VEGF), CD34 progenitor cells and von Willebrand factor (vWF) -expressing mature capillaries, thus increasing capillary density and improving vasodilatory response to exercise [21]. With regard to endothelial dysfunction, CR has been in fact associated to a significant improvement of brachial artery flow-mediated dilation (FMD), as an index of endothelial function [22].

3 Effects of Cardiac Rehabilitation on Functional Capacity

Several studies have shown the efficacy of CR in improving exercise capacity assessed as peak oxygen consumption (peak VO2, higher values corresponding to a greater performance) and ventilatory efficiency determined as ventilation-to-carbon dioxide production ratio (VE/VCO2 slope, lower values corresponding to a greater respiratory function). These cardiopulmonary exercise testing (CPET) parameters have a significant prognostic role in HF [23].

In a study conducted on 58 chronic HF patients with LVEF < 40% CR significantly increased peak VO2 from 14.5 to 17.3 mL/kg/min and improved New York Heart Association (NYHA) functional class [24].

Consistently, Rengo and colleagues demonstrated an improvement of estimated metabolic equivalents (4.6 to 6.2) and peak VO2 (14.4 to 16.4 mL/kg/ min) in 49 HF subjects with mean LVEF 27% who completed 36 sessions of CR [25].

In the ARISTOS-HF (Aerobic, Resistance, InSpiratory Training OutcomeS in Heart Failure) study which enrolled 88 patients with LVEF < 35% and NYHA class II/III the combination of aerobic, resistance and muscle training improved peak VO2, circulatory power, 6-minute walking test distance and QoL and reduced LV end-systolic diameter [26].

In a larger prospective study on 1620 HF patients with LVEF < 35%, ET increased mean peak VO2 from 15.0 to 15.4 mL/kg/min after 3 months. For every 6% increase in peak VO2 after training, the risk of experiencing a combined endpoint of cardiovascular mortality or HF hospitalizations decreased by 8%, and the risk of all-cause mortality was reduced by 7% [27]. Higher baseline exercise capacity was associated with a greater increase of peak VO2 after CR and better prognosis, but a significant risk reduction was also detected in patients with lower baseline values but significant increment of exercise capacity. The lack of improvement of peak VO2 was associated with a two-fold higher risk of death or hospitalization [27]. In the ExTraMATCH II individual patient level meta-analysis, which collected data from 3990 HF patients in 13 studies, CR improved 6-minute walking test distance by 21 m and QoL evaluated by the Minnesota Living with HF Questionnaire by 5.9 points [28].

In a multicenter study conducted on 216 subjects with HFrEF the Rehabilitation Enablement in Chronic Heart Failure (REACH- HF) program improved QoL assessed using the Minnesota Living with Heart Failure questionnaire with a feasible cost- effectiveness [29].

In a study with included 26 patients with HF with preserved EF (HFpEF) who were randomized to receive a 12-week program of inspiratory muscle training (IMT) plus standard care or standard care alone, IMT group improved significantly their maximal inspiratory pressure ($p < 0.001$), peak VO2 ($p < 0.001$), exercise oxygen uptake at anaerobic threshold ($p = 0.001$), ventilatory efficiency ($p = 0.007$), metabolic equivalents ($p < 0{,}001$), 6MWT ($p < 0.001$), and QoL ($p = 0.037$) as compared to the control group [30].

In another population of 64 HFpEF patients who were randomized to ET or usual care alone, ET significantly increased peak VO2 and improved echocardiographic parameters of diastolic dysfunction including E/e' and left atrial volume index [31].

Consistently, in old HFpEF patients (mean age 70 years), ET significantly increased peak VO2 (+2.3mL/kg/min), peak power output, exercise time, 6MWTD, and ventilatory anaerobic threshold (all $p = 0.002$) and improved the physical QOL score [32].

3.1 Recommendations on Exercise Training

On the basis of these evidence, at least 150 min per week of moderate-intensity or 75 min per week of vigorous-intensity physical activity, combined with at least 2 days of muscle-strengthening activity are currently recommended [33]. The target for patients with HF who are clinically stable is to perform aerobic medium-intensity continuous ET for up to 45 min on most days of the week [34]. This target intensity ranges between 70 and 80% of peak heart rate (HR) or 60% of HR reserve consisting in the difference between resting and peak heart rate.

In view of these numerous studies supporting the benefits of CR in patients with variable severity of HF, the availability of additional simple and reliable tools to monitor the effects of CR over time would be of great help. In this regard, this clinical gap could be at least partially covered by a systematic use of cardiac biomarkers.

4 Cardiac Rehabilitation and Cardiovascular Outcomes in Heart Failure: Contrasting Results

From a prognostic viewpoint, different studies have provided contrasting evidence about the effects of ET on cardiovascular outcomes.

The HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study, the largest trial on ET in HF with reduced EF (HFrEF), demonstrated that aerobic ET improved QoL, peak VO2 by 15% and reduced the rates of cardiovascular mortality and HF hospitalizations independent from age, race, sex, etiology, and severity of HF. In this study the improvement of health status was achieved after 3 months and was maintained during the follow-up period [35].

In a study which included 1592 outpatients, those who were assigned to CR had a significant lower risk of the composite outcome of all-cause death and HF rehospitalizations (hazard ratio [HR] 0.77), of all-cause mortality (HR 0.67) and of HF hospitalizations (HR 0.82) [36]. These results were confirmed also in patients with HFpEF and frail subjects and were independent from history of coronary artery disease, hypertension, diabetes, age, sex, and basal natriuretic peptides (NPs) levels [36].

Benefits of ET have been also shown in patients with advanced HF also during mechanical circulatory.

support and early after cardiac transplantation with a significant improvement of health status, treadmill time and leg strength [37].

On the other hand, the randomized multicenter EJECTION-HF (Exercise Joins Education: Combined Therapy to Improve Outcomes in Newly-Discharged HF) trial showed that ET, although safe and feasible, did not reduce the combined endpoint of death or hospital readmission after discharge for acute HF [38].

A meta-analysis of 44 studies enrolling 5783 HF patients showed that CR was able to significantly reduce HF and all-cause hospitalizations by 41% and 30%, respectively, and to improve the Minnesota Living with HF Questionnaire by 7 points [39].

However, the CROS-HF meta-analysis which included 4481 HFrEF-patients did not show significant differences in the effect of CR on mortality and hospitalizations for HF or any reason compared to control-group (not randomized to CR) after 6-month follow-up, despite the improvement in QoL evaluated with both the Kansas City Cardiomyopathy Questionnaire and the Minnesota Living with Heart Failure Questionnaire [40].

Also, an individual-patient-level meta-analysis of 18 studies including 3912 HFrEF subjects showed no significant benefits of CR compared to control-group (subjects who did not undergo CR programs) in terms of all-cause mortality, all-cause and HF hospitalizations [41].

The 2022 Cochrane meta-analysis of 8728 patients demonstrated that CR had neutral effects on overall mortality but significantly reduced the risk of all-cause and HF hospitalizations with concomitant decrease in healthcare costs and improved QoL [42, 43].

An analysis of the HF-ACTION study investigated the factors affecting the effectiveness of ET, suggesting that the use of beta-blockers, pulse pressure, hemoglobin level, electrocardiography findings, body mass index, and history of stroke at baseline potentially influenced the exercise effect on all-cause death and hospitalizations [44].

5 Monitoring the Response to Cardiac Rehabilitation Programs: Role of Biomarkers

Some of the inconsistencies related to the effects of CR on cardiovascular outcomes may be related to the uncertainties linked to the tools to monitor the responses of patients during the course of CR. A multiparametric, comprehensive evaluation is routinely performed during CR programs, including physical examination, blood sampling, echocardiographic and CPET parameters. However, the use of biomarkers has been poorly adopted and characterized during CR. Indeed, biomarker analysis still poses some challenges since single biomarkers might not be exhaustive, reference ranges and variance in absolute and relative values after exercise are not well defined. In addition, specific biomarkers able to represent appropriate and reliable responses to training load, to reflect recovery cycles and to contribute to load management in training settings have not been clearly identified [45]. Indeed, current international guidelines on physical exercise do not provide indications whether to perform seriate measurements of biomarkers to assess the benefits of CR and to guide rehabilitation protocols [10, 34, 46, 47].

5.1 Rational of the Use of Natriuretic Peptides

Since NPs levels are one of the most reliable parameters used to monitor the course of HF [48–51], they might represent the most feasible biomarker to evaluate the efficacy of CR.

NPs levels correlate well with ventricular wall stress and the severity of HF and represent key diagnostic and prognostic markers. Serial measurements of NPs have been demonstrated to be helpful to guide pharmacological and non-pharmacological therapies in HF [52].

An analysis of data from 2137 patients showed that NPs-guided therapy was associated with lower rates of mortality

(-22%) and HF admissions (-20%) compared to symptoms-guided therapy in HFrEF but not in HFpEF [50]. It should be also underlined that comorbidities influenced the results in both HF subsets In HFrEF, the response to NPs-guided therapy was detected in subjects without chronic obstructive pulmonary disease (COPD), diabetes, transient ischemic attack (TIA) and peripheral vascular disease. Although any single comorbidity interaction with treatment efficacy did not.

reach statistical significance, the interaction was significant when comorbidities were considered.

in combination. In HFpEF treatment response was influenced by hypertension and kidney disease [53].

Another study showed that all-cause mortality was significantly reduced by NPs-guided treatment (hazard ratio [HR] 0.62; 95% confidence interval [CI], 0.45–0.86; $p=0.004$] with no interaction with LVEF. However, the survival benefits were seen only in patients aged < 75 years. On the other hand, hospitalizations due to HF (HR 0.80; 95% CI, 0.67–0.94; $p=0.009$) and cardiovascular causes (HR 0.82; 95% CI, 0.67–0.99; $p=0.048$) were significantly lower in NPs-guided patients with no interaction with age or LVEF [54].

5.2 Changes in Natriuretic Peptide Levels During Cardiac Rehabilitation in HF

In the context of CR, the above-mentioned effects on cardiac remodeling, on LV systolic and diastolic function, on neurohormonal and endothelial function and on exercise capacity might account for a potential association between ET and changes in NPs levels. Thus, it appears quite reasonable as well as clinically valuable, to systematically use NPs levels during CR as well as during follow up to strictly monitor the effects of a CR program (Table 1).

In this regard, in a cohort of 928 patients from the HF-ACTION study NT-proBNP and troponin T (TnT) levels were compared in patients who underwent ET or usual care in chronic HF [55]. Median age of the study cohort was 59 years; of these, 63% were white, and 71% were male. Most patients were NYHA class II (67%) or NYHA class III (32%) at study onset, and median LVEF was 25%. Although ET was not associated with significant changes in levels of NT-proBNP, decreases in plasma concentrations of this biomarker were associated with increases in peak VO2 ($P<0.001$) at 3 months and decreased risk of hospitalizations or mortality ($P<0.04$). Patients who were able to perform moderate (3–7 METs per hour/week) and high (> 7 METs per hour/week) exercise activity had a 42% lower risk of mortality and hospitalizations compared to those in the low exercise activity group (< 3 METs per hour/week) but NT-proBNP levels were comparable among groups (853 vs. 762 pg/ml, $p=0.221$) [55].

In a smaller but properly controlled study 85 HF patients were randomized to usual care or CR, consisting in cycling on a bike for a minimum of 3 days per week, 30 min per day keeping heart rate constantly monitored at 65% of peak VO2 heart rate by a wearable device. In those who underwent CR workload, peak VO2 and LVEF increased by 13%, 14% and 9%, respectively. Consistently, BNP levels were reduced by 34% (from 187 to 123 pg/ml), NT-proBNP by 32% (from 1,370 to 929 pg/ml) and norepinephrine by 26% (from 607 to 447 pg/ml) [56]. Peak VO2 was inversely correlated with BNP ($R=0.55$, $p<0.001$), NT-proBNP ($R=0.55$, $p<0.001$), and norepinephrine ($R=0.43$, $p<0.001$),, whereas VE/VCO2 slope directly correlated with BNP ($R=0.61$, $p<0.001$), NT-proBNP ($R=0.54$, $p<0.001$), and norepinephrine ($R=0.43$, $p<0.001$). The change in peak VO2 at the end of the program was correlated with BNP and NT-proBNP changes ($R=0.42$, $p<0.001$ and $R=0.31$, $p<0.01$, respectively), but not with norepinephrine changes. On the other hand, no changes were detected in patients who did not undergo training [56].

In a small study conducted on 19 patients, 12-week exercise program improved stroke volume, QoL and the distance covered by the 6MWT. A reduction of BNP levels was documented in 73% of patients in the exercise group compared to 67% in the control group (patients who did not perform the exercise program) with a trend toward significance [57].

In 61 patients with LV dysfunction after myocardial infarction (MI), with mean age 56 years and LVEF 42%, 6-months training improved workload (+26%, $P<0.001$), peak VO2 (+31%, $P<0.001$) and LV end-diastolic volume index (LVEDVi) (−9%, $P<0.001$) and reduced NT-proBNP levels (−71%, $P<0.001$), with a significant correlation between changes in NT-proBNP and in LVEDVi ($R=0.858$, $P<0.001$) [58].

Consistent results were achieved in a post-MI cohort of 44 subjects, with mean age 55 years and LVEF 45%, in which 3-month ET reduced NT-pro-BNP levels (from 1498 to 470 pg/ml, $p=0.0026$), increased peak VO2 (+4.3 ml/kg per min, $P<0.001$) and exercise work efficiency (+1.3 Power/ml per kg per min, $P<0.001$), showing an inverse correlation between changes in NT-pro-BNP levels and peak VO2 ($R=-0.72$, $P<0.001$) [59].

The effect of aerobic physical training was also evaluated in 90 HF patients on optimal pharmacological treatment, demonstrating an improvement in peak VO2 (from 14.8 to 16.8 mL/kg/min, $p=0.001$), BNP (from 179 to 129 pg/ml) and C-type NP (CNP) (from 7.3 to 5.3 pg/ml) after 9 months [60].

In another study which enrolled 107 HF patients with LVEF ≤ 45, beside the increase in peak VO2 (from 17.8 to 21 mL/kg/min) and the improvement of NYHA class, CR was associated with a 46% decrease in BNP levels (from 276 to

Table 1 Effects of cardiac rehabilitation on cardiac biomarkers

Study	Study design	*N*. of patients	Analyzed biomarkers	Biomarkers changes
HF-ACTION substudy (2014) [55]	Prospective randomized study Supervised exercise program vs. usual HF care	928 with HFrEF	NT-proBNP and cTnT	No significant differences between groups
Passino et al. (2006) [56]	Prospective randomized study CR vs. usual HF care	85 with HfrEF	BNP, NT-proBNP, and norepinephrine	BNP-34%, NT-proBNP −32%, norepinephrine −26% in the CR group
Butterfield et al. (2008) [57]	Prospective randomized study CR vs. usual HF care	19 with HfrEF	BNP	BNP −73% in the exercise group, −67% in the control group with a trend toward significance
Giallauria et al. (2008) [58]	Prospective randomized study CR vs. usual care	61 with LV dysfunction after MI	NT-proBNP	NT-proBNP level reduction (-71%) with a significant correlation with LVEDVi improvement ($R=0.858$, $P<0.001$) in the CR group
Giallauria et al. (2006) [59]	Prospective randomized study CR vs. usual care	44 after MI	NT-proBNP	Inverse correlation between NT-pro-BNP level reduction and improvement of peak VO2 ($R=-0.72$, $P<0.001$). NT-pro-BNP levels from 1498 to 470 pg/ml, $p=0.0026$, peak VO2 +4.3 ml/kg per min, $P<0.001$ in the CR group
Passino et al. (2008) [60]	Prospective randomized study CR vs. HF usual care	90 with HF	BNP and CNP	Reduction of BNP (from 179 to 129 pg/ml) and CNP (from 7.3 to 5.3 pg/ml) in the CR group
Billebeau et al. (2017) [61]	Prospective randomized study CR vs. usual HF care	107 with LVEF < 45%	BNP, galectin-3, sST2, MR-proADM	BNP −46%, galectin-3 -6.3%, sST2 -7.4%, MR-proADM −6.4% in the CR group
Adamopoulos et al. (2014) [62]	Prospective randomized study CR vs. usual care	43 with HFrEF	NT-proBNP	Reduction of NT-proBNP (from 1046 to 790 pg/ML, $p=0.08$) in the CR group
Sarullo et al. (2006) [63]	Prospective randomized study CR vs. usual HF care	60 with LVEF < 40%	NT-proBNP	NT- proBNP levels decreased from 3376 to 1434 pg/ml in the CR group
deFilippi et al. (2012) [64]	Observational study	2933 with HFrEF	NT-proBNP	Highest score of self-reported physical activity was associated with a lower risk of increase in NT-proBNP levels (OR 0.50, 95% CI 0.33–0.77)
Smart et al. (2012) [65]	Meta-analysis of 10 studies	565 with LVEF < 35%	BNP and NT-proBNP	BNP −28.3%, NT-pro-BNP −37.4% after CR
Awada et al. (2024) [77]	Prospective randomized study CR vs. usual HF care	115 after MI	Inflammatory markers	CRP (0.11 vs. 0.21 mg/dL, $p<0.001$), NLR (2.17 vs. 2.26, $p=0.016$) PLR (91.2821 vs. 92.600, $p=0.027$) were significantly lower in the CR group.

See text for abbreviations

129 pg/mL) and in other cardiovascular biomarkers including galectin-3 (-6.3%, $p<0.001$), sST2 (-7.4%, $p=0.036$), mid-regional pro-adrenomedullin (MR-proADM, -6.4%, $p=0.001$) and mid-regional pro-adrenomedullin (MR-pro-ANP) (-16%, $p<0.001$). No change in any biomarker was detected in patients who did not undergo CR. The decrease in BNP was observed regardless of the variation in peak VO2 [61].

In a cohort of 43 patients with HFrEF, mean age 58 years, aerobic exercise significantly improved LVEF (from 28 to

36%, $p=0.005$), LV diameter (from 65 to 64 mm, $p=0.07$), C-reactive protein (CRP) (from 2.8 to 1.4 mg/dL, $p=0.05$) and NT-proBNP (from 1046 to 790 pg/ML, $p=0.08$) [62].

Consistently, another study conducted on 60 subjects with LVEF < 40% in NYHA class II, mean age 53 years, showed that after 3 months the training group experienced an increase in exercise time (from 15.9 to 29.9 min), in peak VO2 (from 14.5 to 17.7 mL/kg/min), in VO2 at the anaerobic threshold (from 12.9 to 15.5 mL/kg/min) and a reduction of NT-proBNP levels (from 3376 to 1434 pg/ml). On the other hand, no significant differences were found in the control group (patients not included in the training program) with respect to baseline parameters [63].

An observational study of 2933 patients with HF found an inverse relationship between NT-proBNP levels and the level of self-reported physical activity [61]. Leisure-time activity was a self-reported measure of weekly energy expenditure in kilocalories quantified by participant responses to a modified Minnesota Leisure-Time Activity Questionnaire that evaluated frequency and duration of 15 different activities during the previous 2 weeks. Compared with participants with the lowest score, those with the highest score had an odds ratio (OR) of 0.50 (95% CI 0.33–0.77) for an increase in NT-proBNP > 25% or > 190 pg/mL after adjusting for comorbidities and baseline levels. A higher activity score associated with a lower long-term incidence of HF [64].

In a meta-analysis of 10 studies including 565 patients with mean age 65 years and LVEF 35%, exercise (training frequency 2–7 weekly sessions, intensity 50–95% of peak VO2, 30–50 min per session) reduced BNP (from 181 to 100 pg/mL,−28%, $p<0.0001$) and NT-pro-BNP (from 1114 to 593 pg/mL, −37%, $p<0.0001$) and improved peak VO2 by 18% ($p<0.0001$). BNP and NT-pro-BNP changes were correlated with those of peak VO2 ($R=-0.31$ and $R=-0.22$, respectively; $p<0.0001$) [65].

Consistent results have been obtained in another meta-analysis of 13 trials that showed a reduction of NT-proBNP (−7412 pg/mL, 95% CI −993.10 to −490.27; $p<0.00001$; I2 = 63%) and VE/VCO2 slope (−3.57, 95% CI −6.48 to −0.67; $p=0.02$; I2 = 97%) with an increase in peak VO2 (3.68 mL/kg/min, 95% CI 2.39–4.96; $p<0.00001$; I2 = 96%), maximal workload (22.80 W, 95% CI 18.44–27.17; $p<0.00001$; I2 = 78%)and systolic function (2.42%, 95% CI 0.64–4.19; $p=0.008$; I2 = 71%) [66].

In a meta-analysis which involved 2563 participants aerobic ET significantly decreased NT-proBNP (standardized mean difference [SMD] -0.229, 95% CI −0.386 to −0.071, $p=0.005$)irrespective of overweight/obesity status but had neutral effects on BNP [67].

The ongoing FUNNEL+study has been designed with the aim to evaluate the efficacy of an exercise and education-based CR program on biomechanical, physiological, and imaging biomarkers in patients with HFpEF and to identify CR responders [68].

5.3 Challenges and Implications of the Use of Natriuretic Peptides

The above-mentioned data, however, derive from small, randomized trials or from observational studies, thus they should be interpreted with caution. In addition, data on the effects of ET on NPs in different subgroups are limited and not exhaustive. Moreover, no information is available about whether there is a minimum cut-off of exercise intensity able to produce significant changes in NPs levels and which biomarker (BNP or NT-proBNP) should be preferred in specific populations. Indeed, few studies have compared the role and the concentrations of BNP and NT-proBNP in HF. Although these biomarkers are considered interchangeable, it has been shown that NT-proBNP levels are relatively higher compared to BNP in women, elderly and subjects with worse kidney function and history of atrial fibrillation, whereas patients with an ischemic etiology of HF had a lower NT-proBNP/BNP ratio [69]. The half-life of BNP is 20 min whereas NT-proBNP has a half-life of 120 min, this explaining why NT-proBNP levels are about six times higher than BNP values, even though these hormones are released in equimolar proportions [70]. BNP is stable in whole blood at room temperature with the addition of EDTA for at least 24 h, while NT-proBNP is stable for at least 72 h at room temperature also without additives. Both BNP and NT-proBNP are stable during freeze and thaw processes [70].

NPs levels might be measured at baseline and with serial assessments during CR programs, with the aim to monitor their correlation with symptoms, anthropometric parameters (e.g. body weight, BP, HR) and functional capacity and thus to adequate exercise intensity in combination with clinical evaluation. NPs modifications during CR might be also associated with potential improvements of the achieved performance, preferably evaluated with CPET. Since higher peak VO2 levels correlate with a lower risk of cardiovascular endpoints across the HF spectrum of LVEF, the potential relationship between NPs reductions and the increase in exercise capacity might be also associated with the improvement in HF prognosis.

Although more focused studies should be encouraged, the use of NPs measurements might contribute to better target and personalize the program of the rehabilitative intervention, representing a cost-effective strategy.

5.4 Potential Future Biomarkers

Different preclinical studies have shown that exercise is associated with the reduction of cardiac fibrosis, inflammation and oxidative stress. Indeed, ET has been demonstrated to decrease the expression of fibrotic genes and signaling such as TGF-b, p-Smad2/3, CTGF, matrix metalloproteinase.

2 and 9, collagen I and insulin-like growth factor (IGF)-1/PI3K/Akt pathway in rats with diabetes and cardiac dysfunction [71, 72]. ET improved cardiac metabolism increasing PGC-1a and Akt activation and reducing the production of mitochondrial reactive oxygen species [73]. As previously mentioned, ET has been associated with the decrease in in the plasmatic levels of galectin 3 and ST2, which represent biomarkers of fibrosis and might be easily measured in clinical practice, also being demonstrated to predict 1-year mortality in HF patients [61].

ET has been also proven to promote vascular relaxation and angiogenesis increasing the expression of nitric oxide synthase and vascular endothelial growth factor receptors [74].

Moreover, other preclinical studies have shown that ET can modulate the immune system increasing.

serum and cardiac interleukin-10, cardiac myeloid derived suppressor cells and leptin receptor and reducing cardiac and circulating leukocytes and cytokine production [75, 76].

Also in a clinical setting of 115 patients with mean age of 55 years who were randomized to ET or standard treatment after MI, inflammatory markers such as CRP (0.11 vs. 0.21 mg/dL, $p<0.001$), neutrophil-to-lymphocyte ratio (NLR) (2.17 vs. 2.26, $p=0.016$) and platelet-to-lymphocyte ratio (PLR) (91.2821 vs. 92.600, $p=0.027$) were significantly lower in the CR group [77].

In addition, ET induced cardiomyocyte-specific miR-222 overexpression and reduced the long noncoding RNA lncExACT1, inhibiting pathological remodeling and dysfunction after ischemic injury [78, 79].

The Exercise aNd hEArt transplant (ENEA) trial is recruiting patients after heart transplant who are being randomized to receive on-site CR followed by telerehabilitation or onsite CR followed by standard homecare and exercise program. The aim of this study is to explore the safety and efficacy of cardiac telerehabilitation after heart transplant and to analyze circulating extracellular vesicles using Surface Plasmon Resonance imaging (SPRi) with a rehabilomic approach [80].

Future studies conducted on HF patients might confirm these beneficial effects of CR and pave the way for suggesting a more systematic use of these biomarkers in clinical practice.

6 Conclusions

Even though a large body of evidence has proven the role of CR as an important tool in the management of HF due to its safety, cost-effectiveness and beneficial effects in terms of QoL and exercise capacity improvement, the participation rates in CR programs are disappointing, since they account for only 10 to 30% of HF patients worldwide. Moreover, contrasting results about the benefits of CR on prognostic outcomes and on the modifications of cardiovascular biomarkers levels during CR can be derived from the available studies. Further trials including larger populations of HF patients with longer follow-up periods are needed to confirm CR as a milestone component of therapeutic strategies for hospitalized and chronic HF patients and to tear down the wall of reluctance and inertia which slows down the widespread diffusion of this tool in clinical practice. In this view, we suggest that systematic assessment of NP levels (or other biomarkers) during CR programs could help to better target and modulate the rehabilitative interventions in order to gain the best clinical outcomes in each individual patient.

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Declarations

Conflict of interest Nothing to disclose.

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