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ORIGINAL RESEARCH ARTICLE

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Effect of multidisciplinary cardiac rehabilitation on the response to cardiac resynchronization therapy

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Summary

Background: Both cardiac resynchronization therapy (CRT) and Multidisciplinary Cardiac Rehabilitation (CR) beneficially influence symptomatic status, exercise capacity, quality of life, and heart failure readmission rates. However, the interaction between both therapies remain incompletely addressed.

Methods: Consecutive CRT patients implanted in a single tertiary care center were retrospectively analyzed. Patients were dived according to the participation in a structured CR-program following CRT-implant. The effect on functional status (New York Heart Association; NYHA-class), reverse remodeling (change in left ventricular ejection fraction; LVEF), and the combined endpoint of heart failure readmission and all-cause mortality was assessed after multivariate correction.

Results: A total of 655 patients were analyzed of whom 223(34%) did and 432(66%) did not participate in a structured multidisciplinary CR-program following implant. No adverse events relating to exercise training occurred during the CR-program. Patients who participated in the CR-program had a more pronounced improvement in NYHA-class at 6-months ($P = 0.006$), even after multivariate correction ($\beta = -0.144$; 95% CI = [−0.270; −0.018]; $P = 0.025$). Maximal workload and VO2max on CPET at 6 months improved significantly even after adjustment ($P < 0.001$, respectively $P = 0.017$). At 6-months, CR associated with more improvement in LVEF (+11.9 ± 13 vs +14.5 ± 11; $P = 0.008$), however, this relationship was lost after multivariate correction ($P = 0.136$). During 36 ± 22 months follow-up, patients in the CR group had a higher event-free survival for the combined endpoint ($P = 0.001$), even after multivariate correction (adjusted HR = 0.547; CI = 0.366-0.818; $P = 0.003$).

Conclusions: Following CRT-implant, the participation in a structured CR-program is safe and beneficially influences symptomatic response and clinical outcome. The beneficial effects of exercise training are potentially independent and additive to the beneficial reverse remodeling effect induced by CRT itself.

KEYWORDS
cardiac resynchronization therapy, clinical outcome, exercise training, functional improvement, response to CRT

1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) significantly improves functional status, exercise capacity, and reduces the occurrence of heart failure hospitalization and all-cause mortality in selected patients with heart failure with reduced ejection fraction (HFrEF).[1-5] By harmonizing cardiac contraction, cardiac output is increased while reducing cardiac filling pressures and functional mitral regurgitation in some, without increase myocardial oxygen consumption.[6] In addition, CRT induces beneficial left ventricular reverse remodeling in most patients.[1-5] These central mechanisms are accepted as the driving force behind the beneficial impact of CRT on outcome. Yet, the heart failure syndrome is a systemic disorder not only characterized by alterations in central hemodynamics, but also by numerous multisystem factors including, metabolic alterations, systemic inflammation, and peripheral abnormalities.[7] A crucial concept explaining the encountered peripheral abnormalities in the heart failure syndrome is the "muscle hypothesis of cardiac failure". This hypothesis states that poor skeletal muscle perfusion activates ergo-receptors leading to neurohormonal activation and peripheral vasoconstriction, hereby stimulating disease progression.[7] Cardiac Rehabilitation (CR) has been shown to improve functional status, quality of life, peak$VO_{2,}$ and reduces heart failure readmission rates.[8] The beneficial effects of CR are mostly attributed to a partial restoration in endothelial function and skeletal muscle abnormalities.[9-12] However, some data even suggest that exercise training could induce left ventricular reverse remodeling.[13] Theoretically, improved central hemodynamics following CRT might allow for better performance during exercise training potentially generating synergism. Small hypothesis generating studies suggested a beneficial link between CR and CRT, illustrating more pronounced improvements in functional status, peak VO2max, and more pronounced changes in left ventricular ejection fraction (LVEF) in some.[13,14] However, larger series confirmation awaits these findings. Additionally, the potential consequences on heart failure admissions or all-cause mortality remain unanswered. This analysis seeks to further clarify the effect of CR following CRT on functional status, left ventricular reverse remodeling and clinical outcome.

2 | METHODS

2.1 | Study population

Consecutive HFrEF patients undergoing CRT-implantation in a single tertiary care center (Ziekenhuis Oost-Limburg, Genk, Belgium) between October 2008 and August 2015, were retrospectively evaluated. CRT indications were in compliance with the European Society of Cardiology guidelines.[15] After implant, all patients underwent a similar pre-specified follow-up and CRT optimization protocol, as published previously by our group.[16,17] Briefly, all patients received identical optimization of heart failure care, including uptitration of neurohormonal blockers, down-titration of loop diuretics, as well as echocardiographic guided AV and VV -optimization of their device settings one day after implantation.[16,18] During the two-day hospital stay for CRT-implantation, the patient was enrolled in a structured ambulatory multidisciplinary CR-program if willing to participate. This analysis studies the impact on functional status, reverse left ventricular remodeling and outcome of patients who did or did not following a CR-program following CRT-implant. The current study is in compliance with the Declaration of Helsinki. Given the retrospective nature of the study design, the need for written informed consent was waived by the local ethical committee. The manuscript was drafted according to the STROBE statement for observational studies.[19]

2.2 | Multidisciplinary cardiac rehabilitation protocol

Following a cardiovascular hospitalization, patients had reimbursement for 45-sessions of supervised ambulatory multidisciplinary CR The first 2 weeks following CRT-implant, the patient was allowed a period of rest to assure optimal healing of the implant site and progressive stabilization of the left ventricular coronary sinus lead. Just before CRT-implant, all patients underwent an outpatient cardiovascular visit with measurement of a baseline cardiac pulmonary exercise test (CPET). Afterward, CR was commenced at a frequency of 3-sessions/week, with each session lasting one hour. After the 45-sessions patients were allowed to continue for 2-sessions/week. The exercise training consisted of both aerobic training with a target heart rate defined as the heart rate achieved at 90% of the ventilator threshold of the CPET during the screening visit. Additionally, resistive training was performed at 50%-80% of one repetition maximum. The intensity of training was increased gradually every two weeks by the supervising physical therapist. All patients completed their exercise training program between 1-month and 6-months following CRT-implant. In addition to the exercise training itself, the multidisciplinary program also offered dietary consultation (salt, diabetes, and calorie restriction if indicated), psychological guidance (anxiety and stress coping, smoking cessation) if necessary, and social support if re-integration into the work field was necessary. At weekly multidisciplinary meetings, the team discussed the progression of the patient. A repeat CPET was performed 6 months after CRT-implant in both patients participating and not participating in the CR-program (part of the CRT-clinic follow-up evaluation).

2.3 | Baseline characteristics and follow-up

Demographics, clinical data just before CRT placement including functional status (New York Heart Association-class: NYHA-class), medical therapy, baseline laboratory results, baseline electrocardiogram, baseline CPET, and echocardiography were retrospectively collected from the individual electronic medical record. Following CRT-implant patients were followed up in a structured multidisciplinary CRT-clinic. Patients received a first follow-up appointment 6 weeks after implantation and a second follow-up at 6 months. Afterward, the follow-up intensity was reduced to once every nine months if clinically stable.

2.4 | Study endpoints

The response to CRT was measured systematically in all patients at 6-months following the CRT-implant. Symptomatic improvement was measured as the change in NYHA-class between implant and

TABLE 1 Baseline characteristics

Variable	Total population (n = 655)	No rehabilitation (n = 432)	Rehabilitation (n = 223)	*P* value
Demographics				
Age, y	72 ± 10	74 ± 9	69 ± 12	<0.001
Octogenarians	166 (25%)	122 (28%)	44 (20%)	0.018
Male	438 (67%)	291 (67%)	147 (66%)	0.710
BMI, kg/m^2		27 ± 5	27 ± 5	0.343
Active smoker	85 (13%)	56 (13%)	29 (13%)	0.391
Cardiomyopathy				
Ischemic	283 (43%)	197 (46%)	86 (39%)	0.081
Non-ischemic	371 (57%)	234 (54%)	137 (61%)	
Comorbidities				
Atrial fibrillation	243 (37%)	164 (38%)	79 (35%)	0.510
Anemia	196 (30%)	136 (32%)	60 (28%)	0.291
Iron deficiency	291 (56%)	193 (57%)	98 (54%)	0.504
COPD	111 (17%)	78 (18%)	33 (15%)	0.465
Hypertension	522 (80%)	348 (81%)	174 (78%)	0.446
Dyslipidemia	462 (71%)	323 (75%)	139 (62%)	0.001
Diabetes	167 (26%)	120 (28%)	46 (21%)	0.055
Stroke	46 (7%)	33 (8%)	13 (6%)	0.382
CKD (GFR <60)	294 (45%)	199 (46%)	95 (43%)	0.398
History valve surgery	89 (14%)	57 (13%)	32 (14%)	0.691
Laboratory analysis				
Sodium, mmol/L	139 ± 10	139 ± 10	139 ± 4	0.670
Hemoglobin, g/dL	13 ± 2	13 ± 2	13 ± 2	0.387
GFR	63 ± 24	61 ± 25	65 ± 24	0.070
NYHA-class				
Class I-II	256 (39%)	172 (40%)	84 (38%)	0.865
Class III	371 (57%)	240 (56%)	131 (59%)	
Class IV	27 (4%)	19 (4%)	8 (4%)	
QRS duration, ms	153 ± 29	154 ± 30	152 ± 28	0.427
LBBB	498 (76%)	336 (78%)	162 (73%)	0.145
Echocardiography				
LVEF, %	30 ± 9	30 ± 10	30 ± 9	0.463
LVEDD, cm	6.0 ± 0.9	6.1 ± 1.0	6.1 ± 1.0	0.993
Medication				
ACE-I or ARB	559 (85%)	360 (83%)	199 (89%)	0.056
Beta-blocker	546 (83%)	352 (82%)	194 (87%)	0.073
Aldosterone antagonist	413 (63%)	266 (62%)	147 (66%)	0.275
Loop diuretic	324 (50%)	222 (51%)	102 (46%)	0.336
Device type				
CRT-pacemaker	337 (52%)	240 (56%)	97 (44%)	0.003
CRT-defibrillator	318 (49%)	192 (44%)	126 (56%)	
Baseline CPET-performance				
Peak power, watts	87 ± 33	87 ± 33	87 ± 35	0.896
VO2max, mL/kg/min	14 ± 5	14 ± 5	15 ± 5	0.172

6-month follow-up. CPET with registration of peak power performance (watts) and VO2max (mL/kg/min) was performed at baseline and at 6 months follow-up in patients undergoing CRT. The change in power performance and VO2max between baseline and follow-up was used as an endpoint of functional improvement. Left ventricular reverse remodeling was defined as the change in Left ventricular ejection fraction (LVEF) between implant and 6-month follow-up. Comprehensive 2-dimensional echocardiography exams were performed (Philips Medical Systems, iE33w) by experienced cardiac sonographers. All reported echocardiography measurements were averaged from three consecutive cycles and assessed as recommended by the American Society of Echocardiography.[20] Left ventricular end-diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF) was obtained using the modified Simpson's biplane method in the apical 2- and 4-chamber view. A combined endpoint of heart failure admission and all-cause mortality was used to measure the effect on outcome.

2.5 | Statistics

Continuous variables are expressed as mean ± standard deviation if normally distributed or median (interquartile range) if non-normally distributed. Normality was checked by the Shapiro-Wilk statistic. Categorical data were expressed as numbers and percentages and compared with the Pearson χ^2-test, or Fisher's exact when appropriate. Continuous variables were compared with the Student's *t* test or Mann-Whitney *U* test as appropriate. Linear regression analysis was used to determine if exercise training independently predicted changes in NYHA-class and LVEF at six months after correction for important covariates. The Kaplan-Meier method was used to construct survival curves, with the log-rank test used for comparison among groups. Cox-proportional hazard modeling was used to assess the adjusted hazard ratio of exercise training on outcome after correction for the same covariates. Statistical significance was always set at a 2-tailed probability level of <0.05. Statistics were performed using SPSS version 22 (IBM, Chicago, IL).

3 | RESULTS

3.1 | Baseline population

A total of 687 patients underwent CRT-implantation, of whom 655 patients (95%) had full data available for the current analysis and formed to study population. Two-hundred-twenty-three patients (34%) participated in a structured exercise training program. The remaining 432 patients (66%) did not opt to participate in a structured training program. Adherence to exercise training was excellent with more than 90% completing the program. However, patients were analyzed in an intention to treat analysis, with all participants starting an exercise training program being assessed in this group. Baseline characteristics of the entire cohorts and subgroups are reflected in Table 1. Some differences in baseline characteristics were present, for instance, patients who did not participate in the exercise training program were older, more often had dyslipidemia and more often received a CRT-pacemaker, with the latter being a signature of more frail population. Not a single patient in the exercise training group developed complications of ventricular arrhythmias or LV lead dislocations secondary to exercise training in the post-CRT-implant period.

3.2 | Functional improvement

At six months follow-up, patients that followed a CR-program were more likely to improve their NYHA-functional class (78% vs 68% had at least improved one NYHA-class; *P* = 0.006, Figure 1). The change in NYHA-class was subsequently approached as a continuous variable and corrected for differences in baseline characteristics and other covariates with a numerical trend toward difference in the exercise and no-exercise group. Following the correction for age, CRT-Defibrillator, ischemic etiology, diabetes mellitus, glomerular filtration rate, dyslipidemia, and baseline use of angiotensin-converting enzyme—inhibitors (or angiotensin-receptor blockers) and beta-blockers, the participation in a CR-program independently predicted more improvement in NYHA-class (β = −0.144; 95% CI = [−0.270; −0.018]; *P* = 0.025). A total of 280 patients (65%) not participating in CR, and 182 patients (82%) participating in CR had both a CPET at baseline and 6 months follow-up. Figure 2 illustrates the improvement in peak power performance and VO2max according to the participation in a CR-program. After adjusting for the aforementioned covariates participation in CR independently predicted more improvement in total power performance (β = 3.77; 95% CI = [3.40; 10.83]; *P* < 0.001) and VO2max (β = 2.37; 95% CI = [0.15; 1.59]; *P* = 0.018) on CPET.

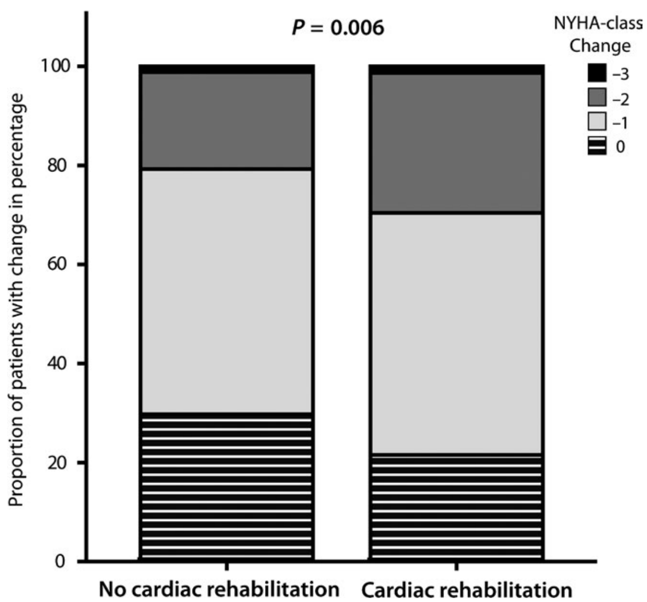

FIGURE 1 Change in NYHA-class

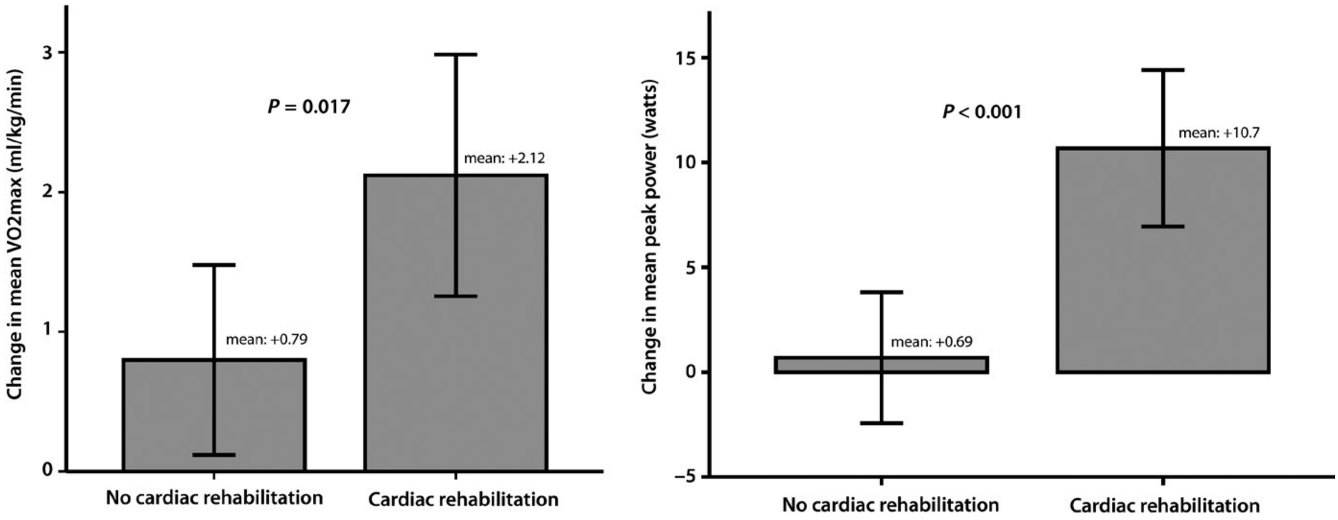

FIGURE 2 Impact of CR on change in VO2max and power performance. Bar graphs with mean and 95% confidence interval

3.3 | Impact on left ventricular reverse remodeling

At six months follow-up, patients who followed a structured CR-program had a more pronounced improvement in LVEF ($P = 0.008$; Figure 3). In a univariate analysis, participation in CR was an univariate predictor of more pronounced change in LVEF (β = 2.536; 95% CI = [0.599; 4.711]; $P = 0.011$). However, after correction for the aforementioned covariates a structured CR-program did not independently predict more left ventricular reverse remodeling following CRT-implant (β = 1.55; 95% CI = [−0.487; 3.585]; $P = 0.136$) in the multivariate model.

3.4 | Impact on clinical outcome

During a mean follow-up of 36 ± 22 months, a total of 147 events for the combined endpoint of heart failure hospitalization and all-cause mortality. A total of 116 events occurred in the group not undergoing exercise training vs a total of 31 events in the group participating in the CR-program. Figure 4 illustrates the Kaplan-Meier curves for both groups, clearly illustrating that patients following a CR-program had a higher degree of event-free survival. In a cox-proportional hazard model, following the correction of the aforementioned covariates, the participation in a structured CR-program was associated with an adjusted hazard ratio of 0.547 (CI = 0.366-0.818; $P = 0.003$) for the combined endpoint of occurrence of heart failure hospitalization or all-cause mortality.

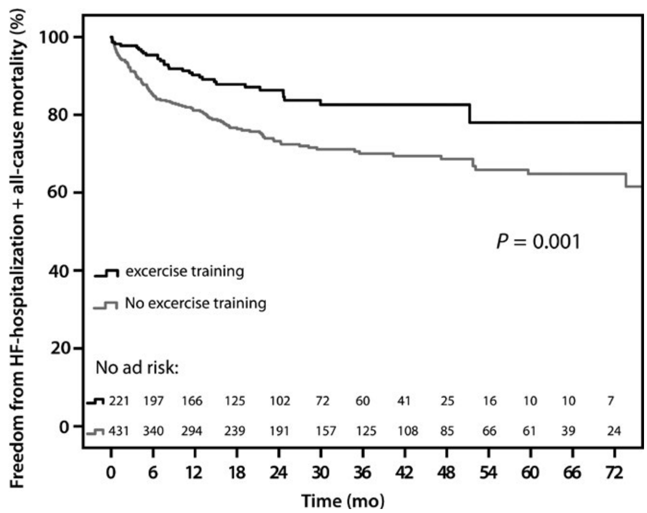

FIGURE 4 Freedom from heart failure hospitalization and all-cause mortality

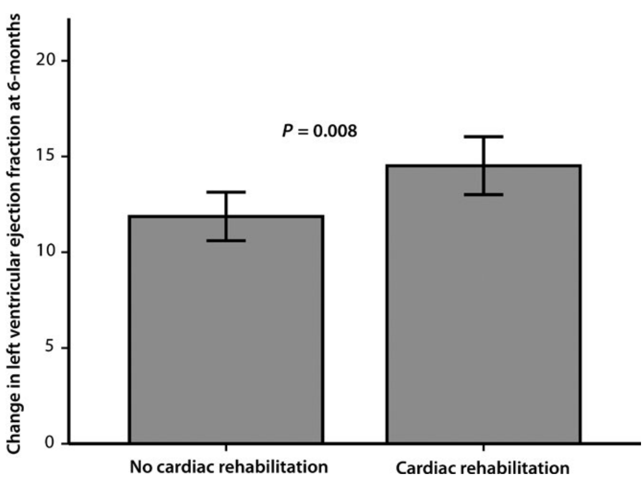

FIGURE 3 Impact of CR on left ventricular reverse remodeling. Bar graphs with mean and 95% confidence interval

4 | DISCUSSION

The current study adds further knowledge about the impact of a multidisciplinary guided ambulatory CR-program following CRT-implant in a large contemporary HFrEF populations. Main findings are: (a) CR following CRT-implant is safe and not associated with device or lead-related complications, (b) CR beneficially influences functional status and clinical outcome, (c) CR is associated with more left ventricular reverse remodeling in univariate analysis but not in multivariate analysis.

The results of the HF-ACTION trial (Heart failure: a controlled trial investigating outcomes on exercise) and several meta-analysis indicate that exercise training results in improvement of exercise tolerance, health-related quality of life, and heart failure readmission rates.[8,21] Exercise training improves endothelial function and reduces total peripheral resistance by upregulating endothelial nitric oxide synthase.[9,12] Furthermore, neurohumoral activation and low-grade inflammation are reduced by exercise training.[9,10] Recently, a microRNA study revealed that responders following CRT had higher levels of circulating microRNAs capable of protecting the myocardium against inflammatory mediators such as TNF-α.[22] This highlights that beneficial reverse remodeling following CRT is also influenced by the environment in which it takes place. One such therapy that might beneficial influence the environment in which reverse remodeling takes place is exercise training.

To the best of our knowledge, two small studies have investigated the effect of a structured exercise training program following the implantation of CRT. Conraads et al illustrated that patients undergoing both CRT and exercise training had a significantly higher improvement in peakVO_2 and higher maximal workload in comparison to patients undergoing CRT but without exercise training.[14] No impact was noted on left ventricular reverse remodeling, however, sample size of the entire study cohort was low (n = 17). Patwala et al on the other hand illustrated in a small (n = 50) hypothesis generating randomized controlled trial that addition of structure exercise training on top of CRT, improves functional status, exercise capacity, quality of life metrics and suggested a more pronounced effect on LVEF.[13] Our study adds further information on this topic in a large contemporary population of optimally treated CRT patients. Our study confirms that adding a multidisciplinary guide CR-program improves functional status (NYHA-class and performance during CPET), even after correction of differences in baseline characteristics or other important covariates. This finding is perhaps not completely surprising if the mechanism of action of exercise training is taken into consideration. Indeed, functional limitation in heart failure is affected by both central and peripheral mechanisms, with the former being mainly targeted by CRT and the latter mainly by exercise training.

The Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) was the first study to document that exercise training results in left ventricular reverse remodeling with a mean improvement in LVEF of 4%.[23] Our CR group also had a more pronounced improvement in LVEF (mean 2.7%). However, after adjustment for difference in baseline characteristics and other covariates, exercise training did not independently predicted more left ventricular reverse remodeling in the post-CRT-implant faze. It is well established that therapies that improve left ventricular reverse remodeling do not always induce symptomatic improvement or vice versa. Additionally, CRT already induces significant reverse remodeling due to the resolution of electromechanical dyssynchrony. Furthermore, as previous published, it is common practice in our CRT-clinic to uptitrate neurohumoral blockers, which also induce further left ventricular reverse remodeling.[24] On this background of significant reverse remodeling it might be difficult to show incremental reverse remodeling attained by exercise training with the current study sample size.

Previous small studies were not designed, in terms of sample size and duration of follow-up, to determine if exercise training following CRT further reduces heart failure readmissions or all-cause mortality.[13,14] The only study that analyzed the interaction between CRT and clinical outcome in patients undergoing exercise training was a retrospective post hoc analysis of HF-ACTION.[25] A total of 435 patients with CRT were included in HF-ACTION of whom 224 patients were randomized to exercise training vs. 211 patients to usual care. In the patients with CRT- vs without a device, the effect of exercise training on the primary outcome endpoint (all-cause mortality +all-cause hospitalization) was not statistically significant. This suggested that exercise training was only capable of demonstrating a reduction in hazard ratio in patients without CRT. However, it might well be that the event rate in the small subgroup of patients implanted with CRT was too limited to potentially demonstrate a hazard ratio reduction induced by exercise training. In contrast, we did not compare patients with vs without a CRT-device exposed to exercise training. In our study, patients with CRT who participated in a CR-program had a statistically better event-free survival than those who did not. Interestingly, after correction for the same covariates which resulted in the diminution of CR on left ventricular reverse remodeling, CR remained independently associated with a reduction in heart failure hospitalization and all-cause mortality. This lends credence to the hypothesis that following CRT-implant CR induces beneficial effects on functional status and outcome which might not be mediated by central mechanisms (reverse remodeling) but by other independent and additive (perhaps peripheral) mechanisms.

5 | LIMITATIONS

First, this is a retrospective analysis looking at the impact of CR following CRT, as patients were not randomized the results should be interpreted as hypothesis generating. Causality in a retrospective study is difficult to defer, and unregistered covariates might impact the found associations. Secondly, a small number of patients were excluded due to missing of pivotal data; however, these patients were missing at random. Thirdly, in a retrospective analysis, it is difficult to decipher how many sessions of exercise training were followed by the small group of patients not completing the entire exercise program. However, it is common practice to include these patients in the group they were initially enrolled in, such as performed in an intention to treat analysis in randomized controlled trials. Finally, some differences were present in baseline characteristics which could explain a lower penetration of CR (which are potentially not amenable for change). For instance, patients who did not follow at CR-program were more likely to have received a CRT-P, which in clinic practice often hints to a higher comorbidity burden. This was also reflected in the higher age of patients not participating in the CR-program.

6 | CONCLUSION

Following CRT-implant, the participation in a structured exercise training program is safe and beneficially impacts functional response and clinical outcome. These beneficial effects might span beyond the central mechanism of reverse remodeling induced by CRT itself. Hereby, underscoring the complimentary role of exercise training in CRT patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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