


The impact of exercise training for chronic heart failure patients with cardiac resynchronization therapy

A systematic review and meta-analysis

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Abstract

Background and objective: Systematically review the current published literature on the impact of exercise training (ET) in chronic heart failure (CHF) patients who were conducted cardiac resynchronization therapy (CRT).

Methods: PubMed, EMBASE, and the Cochrane Library of Controlled Trials databases were searched for trials comparing the additional effects of ET in CHF patients after CRT implantation with no exercise or usual care control up until 2020.03.07. We independently screened the literature, extracted data, employed the tool for the assessment of Study quality and reporting in EXercise (TESTEX) to evaluate study quality and risk of bias, and performed meta-analysis with Revman 5.3 software.

Results: Eight trials were identified for qualitative analysis and 7 randomized controlled trials (RCTs) included 235 participants (120 ET; 115 controls) for quantitative analysis. The results showed that the maximal workload (mean difference [MD] 26.32W, 95% CI 19.41–33.23; $P < .00001$, $I^2 = 0\%$) and the exercise duration (MD 68.95 seconds, 95% CI 15.41–122.48; $P = .01$, $I^2 = 76\%$) had significant improvement in the ET group versus control. Subgroup analysis showed that compared with control, the change in peak oxygen uptake (VO_2) (MD 3.05 ml/kg/minute, 95% CI 2.53–3.56; $P < .00001$, $I^2 = 0\%$), left ventricular ejection fraction (LVEF) (MD 4.97%, 95% CI 1.44–8.49; $P = .006$, $I^2 = 59\%$), and health related quality of life (HRQoL) (the change in Minnesota living with heart failure questionnaire [MLHFQ]: MD –19.96, 95% CI –21.57 to –18.34; $P < .00001$, $I^2 = 0\%$) were significantly improved in the light to moderate intensity training (non-HIT) group, while there seemed no statistical difference of above endpoints in the high intensity training (HIT) group.

Conclusion: During the short term (up to 6 months), non-HIT could improve exercise capacity, cardiac function, and HRQoL in CHF patients with CRT. However, due to the small number of participants, a high-quality large-sample multicenter trial is demanded.

Abbreviations: 6-MWT = six-minute walk test, CHF = chronic heart failure, CRT = cardiac resynchronization therapy, ET = exercise training, HFrEF = heart failure with reduced ejection fraction, HIT = high intensity training, HRQoL = health related quality of life, LBBB = left bundle branch block, LVEF = left ventricular ejection fraction, MD = mean difference, METs = metabolic equivalents, MLHFQ = Minnesota living with heart failure questionnaire, NHP = Nottingham Health Profile, NYHA = New York Heart Association, RCT = randomized controlled trial, SCD = sudden cardiac death, SMD = standard mean difference, TESTEX = tool for the assessment of Study quality and reporting in EXercise, VO_2 = oxygen uptake.

Keywords: cardiac resynchronization therapy, exercise training, heart failure, meta-analysis

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1. Introduction

Chronic heart failure (CHF) is a complicated syndrome characterized by impaired health related quality of life (HRQoL) and exercise intolerance due to structural and/or functional cardiac abnormalities.^[1] It affects approximately 1% to 2% of people in the developed countries and the incidence mainly increases with age.^[2] After a clear diagnosis, the 5-year and 10-year survival rates were 50% and 10%, respectively.^[3] Besides, CHF patients are likely to have left ventricular dyssynchrony, which will increase the risk of sudden cardiac death (SCD).^[4] And some studies have shown that left ventricular dyssynchrony was related to the greater impairments in regional myocardial perfusion and sympathetic activity, which likewise increase the SCD risk.^[5–7]

Cardiac resynchronization therapy (CRT) is a standard therapeutic strategy for symptomatic CHF patients and asymptomatic HF patients with cardiomyopathy with left bundle branch block (LBBB).^[8] Compared with optimal pharmacologic therapy alone, numerous evidences from clinical trials have certified that all-cause mortality, morbidity, and first hospitalization would decrease with CRT. Furthermore, it significantly lightens symptoms and raises exercise capacity and quality of life in CHF patients.^[9,10] These benefits are basically due to an improvement of central hemodynamics. Improved central hemodynamics has its ability to harmonize cardiac contraction, reduce mitral regurgitation, reverse left ventricular remodeling, and continuously enhance left ventricular ejection fraction (LVEF).^[8] However, despite the amelioration, all major trials have shown a 20% to 40% non-response rate that is mainly reflected by the change of left ventricular reverse remodeling and LVEF 3 to 6 months after CRT implantation. The external contributors of the non-responder are principally due to men, low exercise capacity, ischemic cardiomyopathy, suboptimal medical therapy, etc.^[11] Patwala and his colleagues speculated that the non-responder might also reflect CRT only improves the central hemodynamic status; however, a large proportion of CHF patient symptoms are peripheral factors.^[12]

In CHF patients, the peripheral mechanisms focus on impaired metabolic vasodilation and reduced skeletal muscle function which causes decreased exercise endurance and make a progression of symptom.^[13] It is already recognized that exercise training (ET) makes an impact on the treatment of CHF patients, including reduction in morbidity and mortality,^[14] prevention of left ventricular remodeling,^[15] minimizing readmission, improving quality of life,^[16] besides, increasing 20% exercise tolerance on average.^[17] Reasonably, the benefits of ET in CHF patients show a complex combination of central and peripheral mechanisms,^[18] improving not only left ventricular function, but also skeletal muscle neovascularization and endothelial function.^[19] Above all, despite CRT can improve the central effects of CHF patients, it seems to have little improvement on skeletal muscle function. After CRT implantation, superimposing ET on CHF patients may further improve the exercise performance. Therefore, our objective was to systematically review the current published literature on the additional impacts of ET on CHF patients after CRT implantation.

2. Methods

2.1. Literature sources and searches

According to the PRISMA guidance,^[20] we systematically performed a literature search in PubMed, EMBASE, and the Cochrane Library of Controlled Trails databases for studies

exploring the additional effects of ET in CHF patients conducted CRT, up until 7 March 2020. The following keywords were used in various combinations: cardiac resynchronization therapy, atrio-biventricular pacing, biventricular pacing, cardiac rehabilitation, exercise training, physical activity, and physical fitness. In addition, systematic review, meta-analysis, and reference list were manually searched for additional study interests.

2.2. Study selection criteria

Screening process of studies is outlined in Figure 1. The predetermined inclusion criteria contained:

- (1) studies assessing the impact of ET on CRT recipients;
- (2) standard therapy including no exercise or usual care for comparison;
- (3) studies reporting complete data on intervention and control groups;
- (4) ET duration of at a minimum 8 week; and
- (5) enrolled adult CHF patients (>18 years old).

Exclusion criteria included:

- (1) abstracts, case studies without raw data or analysis, reviews, editorials, comments, and meta-analysis;
- (2) non-English language published;
- (3) studies lacking endpoint assessments such as peak oxygen uptake (VO₂) (peak oxygen uptake).

2.3. Data extraction and management

Two reviewers independently retrieved the literature. After excluding studies that were clearly incompatible with the inclusion criteria, read full text of the possible conforming studies and determined whether they really met the inclusion criteria, then, cross-checked. Disagreements were resolved by joint discussion or a third author's review. If necessary, contacted the original study author via email or telephone for undetermined but important information about this review. From selected studies, 2 other reviewers extracted data in accordance with the designed extraction data sheet. The contents included:

- (1) first author's name, year of publication, study design, and sample size;
- (2) CHF patient clinical and demographic information (e.g., mean age or gender);
- (3) exercise intervention details: type (resistance/aerobic/com-bined), session duration, frequency, intensity, and modality;
- (4) follow-up duration and measurement period;
- (5) concerned binary and continuous outcomes including exercise capacity (peak VO₂, exercise duration, maximal workload, the metabolic equivalents (METs), six-minute walk test (6-MWT), etc), cardiac function (represented by LVEF), HRQoL (Minnesota living with heart failure questionnaire [MLHFQ], Nottingham Health Profile [NHP], a Portuguese version of the HeartQoL, etc), New York Heart Association (NYHA) class, and adverse events;
- (6) key elements of risk of bias;
- (7) intervention compliance and adverse events.

2.4. Study quality

Two independent evaluators assessed study quality by employing the Tool for the assessment of Study quality and reporting in Exercise (TESTEX) scale: a 12 criteria with a maximum score of

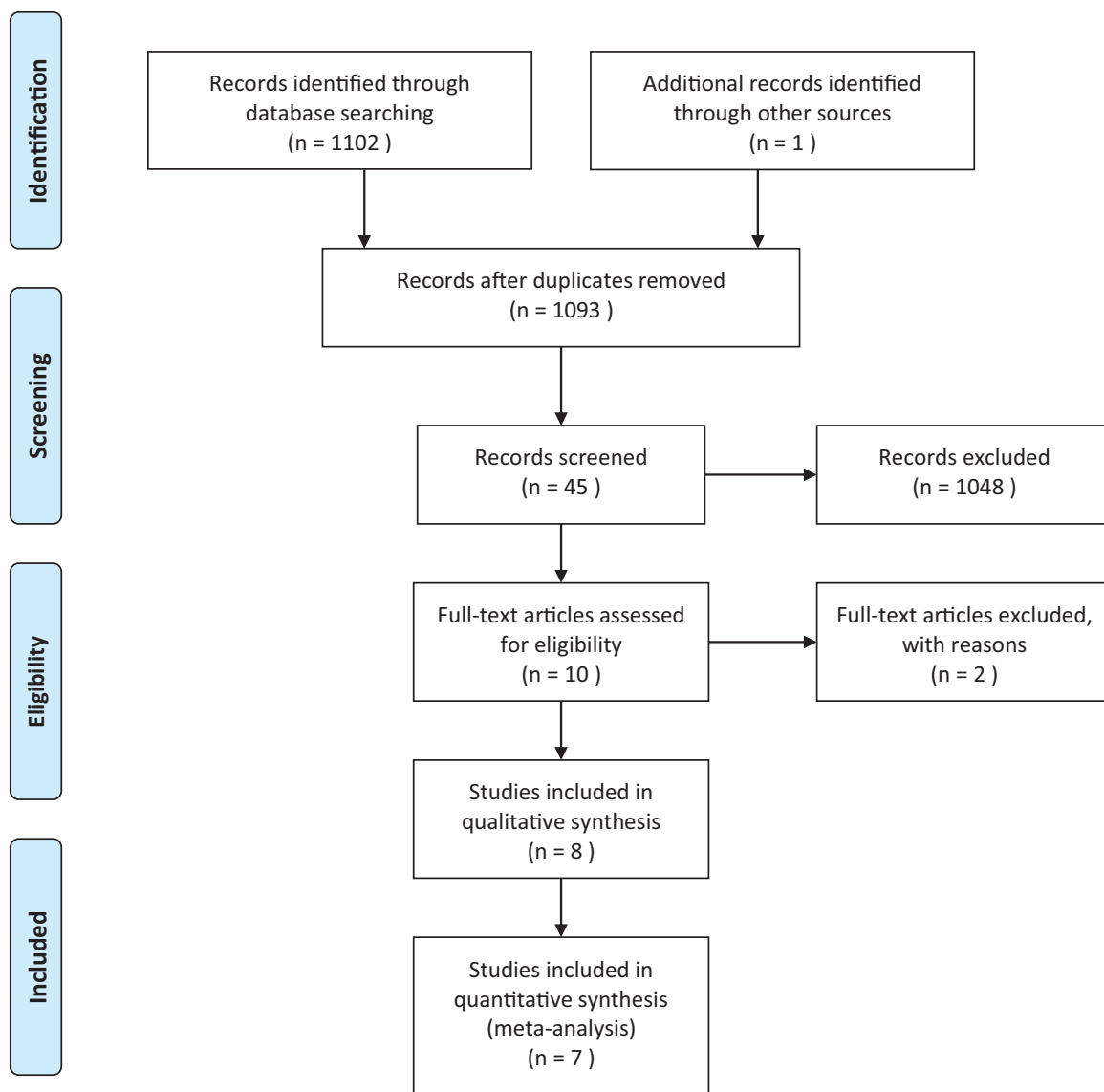


Figure 1. PRISMA flowchart of study selection process.

15 points scale to assess the study quality (up to 5 points) and reporting (up to 10 points), which is specifically suitable for exercise training studies.^[21] A study quality <10 points was considered low quality.

2.5. Statistical analysis

The RevMan V.5.3 software provided by Cochrane Collaboration was used for quantitative analysis. For binary variables, we applied risk ratio and its 95% CI, and mean difference (MD) or mean baseline follow-up change as well as SD were used for continuous variables. When the mean change and its SD were not reported, the former was calculated by the subtraction from baseline to follow-up, and SD could be calculated using RevMan V.5.3 from the number of participants in each group and between or within groups *P*-value or 95% CI. When the exact *P* values were not provided, it was expressed by a preset value, for example, *P* < .05 turned into *P* = .049, *P* < .01 turned into *P* = .0099 and *P* = not

significant turned into *P* = .051. In the continuous variable data, standard mean difference (SMD) was used when the same outcome was measured in different ways; otherwise, we exerted MD. *I*² test was used to quantify the statistical heterogeneity, when over 25%, 50%, and 75% representing low, medium, and high heterogeneity, respectively. The endpoints of training and control in CHF patients with CRT were analyzed with random-effects models. When there was clinical heterogeneity (*I*² ≥ 50%) between groups, firstly, we performed the sensitivity analysis, comparing the results of all studies with those excluding individual studies at high risk of bias. Then we divided the subgroups according to possible causes, such as sex, age, weight status, exercise pattern, etc. If unexplainable heterogeneity still existed between groups after the subgroup analysis, a descriptive analysis was performed. When studies reported multiple measurement time points, the most recent data after the end of intervention was extracted. Publication bias was visually determined by funnel plots. Ethical approval is not required because although the research subjects involved are

human beings, this systematic review and meta-analysis is a secondary analysis based on previous published studies.

3. Results

Studies were published from 1999 to 2020, and 1103 records were initially identified in the extensive database. After duplicates removing and title exclusion, 45 abstracts were screened, of which 10 articles were assessed for eligibility in full texts. We excluded 2 studies that did not meet the primary inclusion criteria. Of the remaining 8 studies, 7 were randomized controlled trial (RCTs)^[12,22–27] and 1^[28] was a retrospective case–control study that did not provide complete outcome data. Therefore, we applied qualitative analysis in these 8 studies and quantitative analysis in 7 RCTs.

3.1. Study characteristics

Seven RCTs consisted of 235 participants, of which 120 participants were assigned to the ET group and 115 to the control group. The mean duration of follow-up was varied, ranging from 5 to 24 months (mean=10). Unlike others were supervised exercise, 1 study combined hospital-based with home-based ET.^[24] As regards exercise intensity, there was a considerable heterogeneity between studies. On the basis of guideline,^[29] when the peak VO₂ is ≥85% or the peak heart rate is ≥90%, it belongs to the high exercise intensity (HIT). And while the peak VO₂ is from 20% to 60% or the ET can be sustained for more than 30 minute, it is a light to moderate exercise intensity (non-HIT). In our review, 3 RCTs^[12,26,27] compared HIT with control, while the intervention groups of other 4 RCTs^[22–25] were light to moderate exercise training. More details of study characteristics were summarized in Table 1.

3.2. Study quality and risk of bias

According to the TESTEX scale, except that 2 studies separately conducted “intention-to-treat analysis”^[26,28] and “activity monitoring in control groups”^[24,25] items (<50%), the achievement of other criteria was all equal to or above 50%. One study^[28] had a TESTEX score below 10, and the average score for all the studies was 10.75 (range: 9–12). Table 2 completely listed the TESTEX scores for each study in detail.

3.3. Qualitative analysis

Exercise capacity and cardiac function were the most common endpoints. For exercise capacity, all studies reported peak VO₂ and 87.5% of them had a significant improvement with ET compared to the control. Else exercise capacity outcome measures included exercise duration, maximal workload, the METs, and 6-MWT. Except that, 1 study^[27] had no statistical improvement in exercise duration, other endpoints were all significantly improved within the ET group. For cardiac function, all studies reported LVEF and 62.5% of them showed LVEF was significantly superior in the ET groups. Other endpoints contained HRQoL^[12,22–24,26,27] (performed studies, n=6) and NYHA functional class^[12,22,23,26,28] (n=5). 83.3% and 100% of these studies were significantly improved within ET groups, respectively. When reporting HRQoL, 1 study^[24] assessed the NHP, 1 study^[26] measured a Portuguese version of the HeartQoL, and the other 4 studies used the MLHFQ for

evaluation. Three studies^[12,22,27] reported that participants in the ET group did not occur any adverse events during the intervention period. In the 18-month follow-up, Smolis-Bąk et al found that the mortality and hospital admissions between groups were similar.^[24] While Martens et al reported 116 control and 31 ET participants of all-cause mortality and hospitalization for heart failure during an average follow-up of 36±22 months,^[28] and the adjusted hazard ratio of ET was 0.547 (95% CI 0.366–0.818; *P*=.003).

3.4. Quantitative analysis

3.4.1. Exercise capacity. Six studies reported the change in peak VO₂. Subgroup analysis was performed to assess the exercise capacity of different exercise intensity among participants in the ET group. Three studies adopted light to moderate intensity training which was represented by non-HIT, and pooled analysis showed that compared with control, peak VO₂ in the non-HIT group was significantly improved (MD 3.05 ml/kg/minute, 95% CI 2.53–3.56; *P*<.00001, *I*²=0%). Three studies exercised HIT modality, and the result showed no statistical difference in the change of peak VO₂ between intervention and control group (MD 0.80 ml/kg/minute, 95% CI –0.07 to 1.68; *P*=.07, *I*²=56%) (Fig. 2). Three studies reported the maximal workload, and pooled analysis showed the ET group had a statistically significant improvement versus the control group (MD 26.32 W, 95% CI 19.41–33.23; *P*<.00001, *I*²=0%) (Fig. 3). As 4 studies reported the exercise duration, it was significantly improved in the ET group compared to control (MD 68.95 seconds, 95% CI 15.41–122.48; *P*=.01, *I*²=76%) (Fig. 4).

3.4.2. Cardiac function. Six studies reported LVEF. According to the subgroup analysis based on exercise intensity, 3 studies exercised the non-HIT modalities, and pooled analysis showed that participants with non-HIT had a statistically significant increase in LVEF compared with control (MD 4.97%, 95% CI 1.44–8.49; *P*=.006, *I*²=59%). The other 3 studies exercised HIT modality, and the result showed no statistical difference in LVEF between control and the HIT groups (MD –0.72%, 95% CI –4.72 to 3.28; *P*=.73, *I*²=70%) (Fig. 5).

3.4.3. HRQoL. Four studies reported the change in MLHFQ. Two studies applied the non-HIT modalities, and the integrated result showed that participants in the non-HIT group had a lower MLHFQ than in the control group, meaning a significant improvement in HRQoL (MD –19.96, 95% CI –21.57 to –18.34; *P*<.00001, *I*²=0%). The other 2 studies applied the HIT modalities, and the result indicated no statistical difference in the change of MLHFQ between intervention and control groups (MD 4.48, 95% CI –27.79 to 36.75; *P*=.79, *I*²=84%) (Fig. 6).

3.4.4. NYHA class. Four studies reported the change in NYHA class and there was no statistical difference between intervention and control groups (MD –0.75, 95% CI –1.60 to 0.11; *P*=.09, *I*²=93%) (Fig. 7).

3.4.5. Publication bias. There was no evidence of publication bias in the selected studies employing funnel plots.

4. Discussion

This systematic review and meta-analysis suggest that exercise with light to moderate intensity significantly improves exercise

Table 1

Characteristics of included studies.

Study	Design	Patients' information	Intervention	Measurement period	Outcome	Adverse event
Belardinelli et al (2006)	RCT	15 (ICD-CRT with ET): 10 (ICD-CRT without ET)	Supervised exercise for 8wk, 3 sessions/wk at 60% of peak VO ₂ . Each session lasted about 1h.	Baseline and 8wk (the day when the completion of the training program)	Peak VO ₂ , cardiac volumes and function, MLHFQ and LVEF	8 controls had sustained ventricular tachycardia, while no trained patients had adverse events.
Conraads et al (2007)	RCT	8 (CRT with ET): 9 (CRT without ET)	Supervised ambulatory exercise for 4 mo, 3 sessions/wk as the heart rate achieved at 90% of the ventilatory threshold during CPET, each lasting for 1h.	Baseline, 1 mo and 5 mo after CRT implanted	Peak VO ₂ , maximal workload, circulatory power, VO ₂ AT, Watt AT, LVEF, NYHA class, NT-pro BNP, and MLHFQ	No patients had complications from the exercise training, and there were no cardiac arrhythmias.
Patwala et al (2009)	RCT	25 (CRT with ET): 25 (CRT without ET)	Physician-supervised exercise program for 3 mo and 3 sessions/wk at 80% of the peak heart rate for the first 4wk, 85% for the next 4wk, and 90% for the final 4wk, each lasting for 30min.	Before and 3 and 6 mo after CRT implanted	Peak VO ₂ , NYHA functional class, exercise duration, MLHFQ, peak cardiac power output, respiratory exchange ratio, and LVEF	
Smolis-Bąk et al (2015)	A randomized, prospective observation	26 (CRT with ET): 26 (CRT without ET)	Hospital-based and home-based exercise training for 8 wk plus hospital stay, 5 sessions/week at low intensity of home-based exercise training.	Prior to CRT implantation and after 3–4 and 12mo	0, 3–4, 12 mo; peak VO ₂ , AT, METs, and treadmill test duration, 6-MWT, Beck Depression Inventory, and NHP. 0, 12 mo: standard echocardiography	Up to 18 mo, there were 3 cases of death (9.4% in the CRT-Ex group and 3 cases of death in the CRT-Control group (10.3%) (P=1.0). There were 14 (43.8%) and 15 (51.7%) hospital admissions in the CRT-Ex and CRT-Control groups, respectively (P= .5334).
Nobre et al (2016)	RCT	23 (CRT with ET): 22 (CRT without ET) randomized. 14 (CRT with ET): 16 (CRT without ET) analyzed	Supervised exercise for 4 mo 3 sessions/week, each lasting for 1 h. The exercise intensity was established by heart rate levels that corresponded to anaerobic threshold up to 10% below the respiratory compensation point obtained in the CPET.	1 mo and 5 mo after CRT implantation	Peak VO ₂ exercise duration, workload, and LVEF MSNA burst frequency and burst incidence, FBV and FVC Na/Ca _v 2 exchange relative expression and Ryanodine receptor expression	
Martens et al (2018)	Retrospective case-control study	223 (CRT with ET): 432 (CRT without ET)	Supervised cardiac rehabilitation for 45 sessions, 3 sessions/wk, as the heart rate achieved at 90% of the ventilator threshold of the CPET, each lasting for 1h. The intensity was increased gradually every 2 wk.	Before CRT-implant and 6 mo after CRT-implant.	NHFA-functional class, peak VO ₂ , LVEF	During a mean follow-up of 36 ±22 mo, 116 events occurred in the control group vs 31 events in the CR group.
Santa-Clara et al (2019)	RCT	34 (CRT with HIT): 29 (CRT without HIT) randomized. 20 (CRT with HIT): 17 (CRT without HIT) analyzed.	Supervised, hospital-based, HIT for 24 wk, 2 sessions/wk at 90–95% peak heart rate, each for 60 min.	Before and at 6 mo after CRT implantation	HRQoL (a Portuguese version of the HeartQoL), NYHA class, Peak VO ₂ , CPET duration, Peak HR, HR recovery 1' (bpm), LVEF, LV mass	
Spee et al (2019)	RCT	12 (CRT with HIT): 12 (CRT without HIT)	Supervised HIT for 3 mo, 3 sessions/wk with a workload corresponding to 85–95% of peak VO ₂ , each lasting for about 40min.	Before and at 3 and 6 mo after CRT implantation	HRQoL (MLHFQ), LVEF, peak VO ₂ , and peak workload	No adverse cardiovascular events occurred during exercise testing and high intensity interval training sessions.

6-MWT = six-minute walk test, AT = anaerobic threshold, CHF = chronic heart failure, CPET = cardiopulmonary exercise testing, CR = cardiac rehabilitation, CRT = cardiac resynchronization therapy, ET = = exercise training, FBV = forearm blood flow, FVC = forearm vascular conductance, HIT = high-intensity interval training, HRQoL = health related quality of life, ICD = implantable cardioverter defibrillators, LVEF = left ventricular ejection fraction, METs = metabolic equivalents, MLHFQ = Minnesota living with heart failure questionnaire, MSNA = muscle sympathetic nerve activity, NT-proBNP = NT-pro brain natriuretic peptide, NYHA = New York Heart Association.

Table 2
Assessment of study quality and risk of bias employing TESTEX.

Study	Eligibility criteria specified	Randomization specified	Allocation concealment	Groups similar at baseline	Blinding of assessor	Outcome measures assessed in 85% of patients*	Intention-to-treat analysis	Between-group statistical comparisons reported†	Point measures and measures of variability	Activity monitoring in control groups	Relative exercise intensity constant	Exercise volume and energy expenditure	Total TESTEX (/15)
Belardinelli	1	1	0	1	1	2	0	2	1	0	0	1	10
Conraads	1	1	1	1	1	1	0	2	1	0	1	1	11
Patwala	1	1	1	1	0	2	0	2	1	0	1	1	11
Smolis-Bak	1	1	1	0	0	2	0	2	1	1	1	1	11
Nobre	1	1	1	1	1	1	0	2	1	1	1	1	12
Martens	0	0	0	0	0	3	1	2	1	0	1	1	9
Santa-Clara	1	1	1	1	0	1	1	2	1	0	1	1	11
Spee	1	1	1	0	1	3	0	2	1	0	0	1	11
Total	7	7	6	5	4	8	2	8	8	2	5	8	

TESTEX=tool for the assEssment of Study quality and reporting in EXercise.

* Three points total – 1 point if adherence >85%, 1 point if adverse events reported, and 1 point if exercise attendance reported.

† Two points total – 1 point if primary outcome reported, and 1 point if all other outcomes reported.

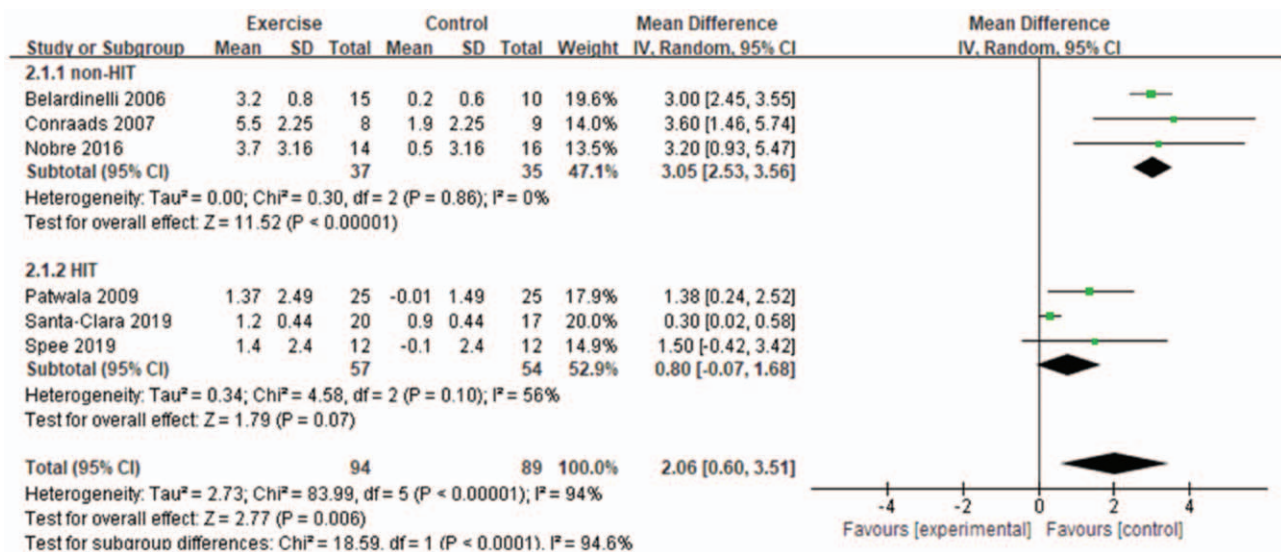


Figure 2. Impact of non-HIT and HIT on the change of peak VO₂ in CHF patients with CRT. CHF=chronic heart failure, CRT=cardiac resynchronization therapy, HIT=high intensity training, non-HIT=light to moderate intensity training, VO₂=oxygen uptake.

capacity, cardiac function, and HRQoL in CHF patients who undergo CRT implantation during a short-term follow-up, compared to the control group with no exercise or usual care. Our analyses evaluated a total of 8 studies containing 7 RCTs and including 235 participants. The present study innovatively employed the TESTEX to analysis study quality and risk of bias. And our qualitative analysis found that compared to

control, both HIT and non-HIT modalities would not increase the hospitalization and mortality of CHF patients with CRT implantation. Most importantly, this current review compared the different effects of HIT and non-HIT on outcomes. We analyzed 6 endpoints, including the change in peak VO₂, exercise duration, maximal workload, LVEF, the change in MLHFQ, and the change in NYHA class. The first 5 items of non-HIT groups

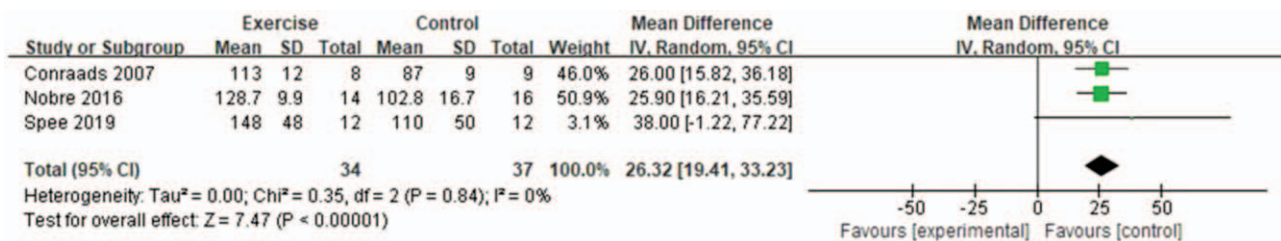


Figure 3. Impact of non-HIT and HIT on the maximal workload in CHF patients with CRT. CHF=chronic heart failure, CRT=cardiac resynchronization therapy, HIT=high intensity training, non-HIT=light to moderate intensity training.

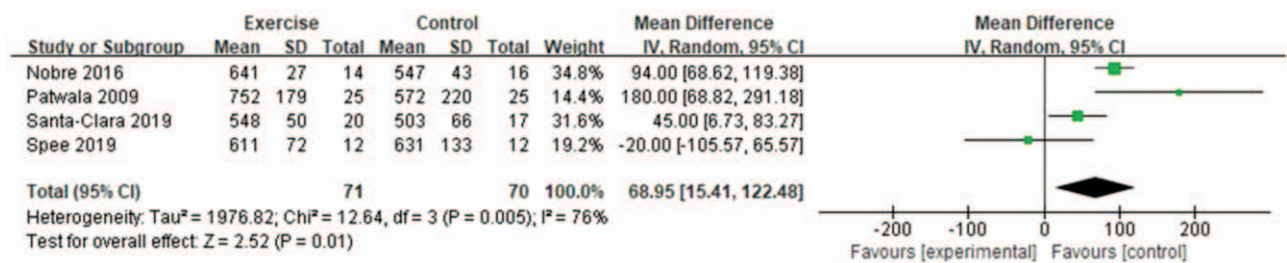


Figure 4. Impact of non-HIT and HIT on the exercise duration in CHF patients with CRT. CHF=chronic heart failure, CRT=cardiac resynchronization therapy, HIT=high intensity training, non-HIT=light to moderate intensity training.

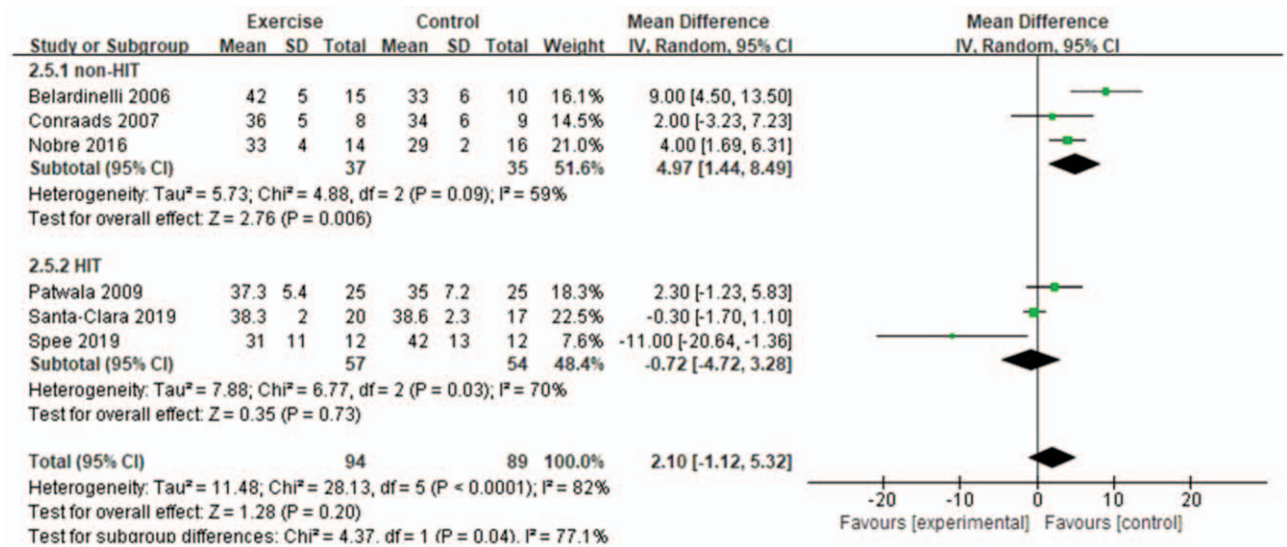


Figure 5. Impact of non-HIT and HIT on LVEF in CHF patients with CRT. CHF=chronic heart failure, CRT=cardiac resynchronization therapy, HIT=high intensity training, LVEF=left ventricular ejection fraction, non-HIT=light to moderate intensity training.

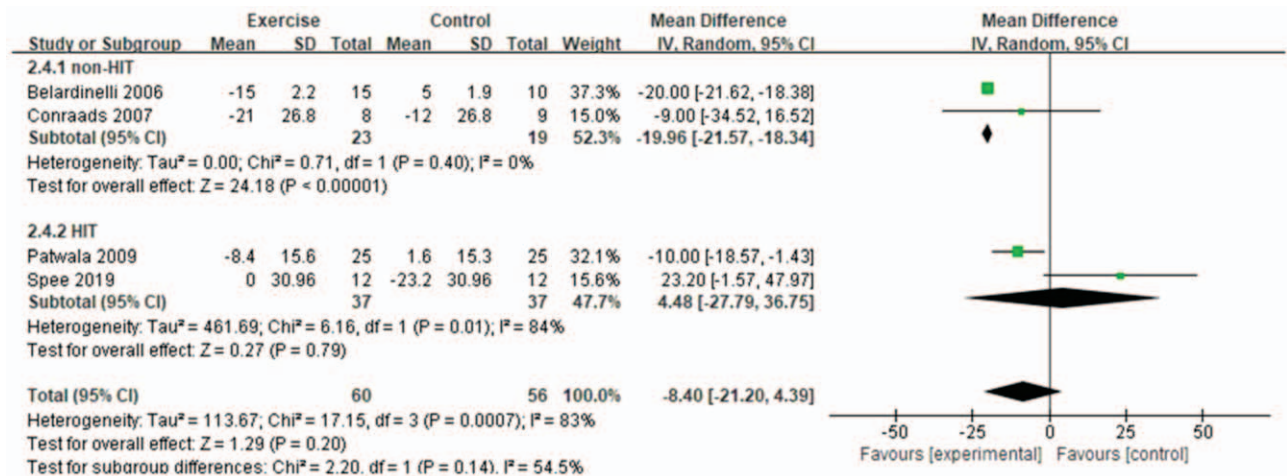


Figure 6. Impact of non-HIT and HIT on the change of MLHFQ in CHF patients with CRT. CHF=chronic heart failure, CRT=cardiac resynchronization therapy, HIT=high intensity training, MLHFQ=Minnesota living with heart failure questionnaire, non-HIT=light to moderate intensity training.

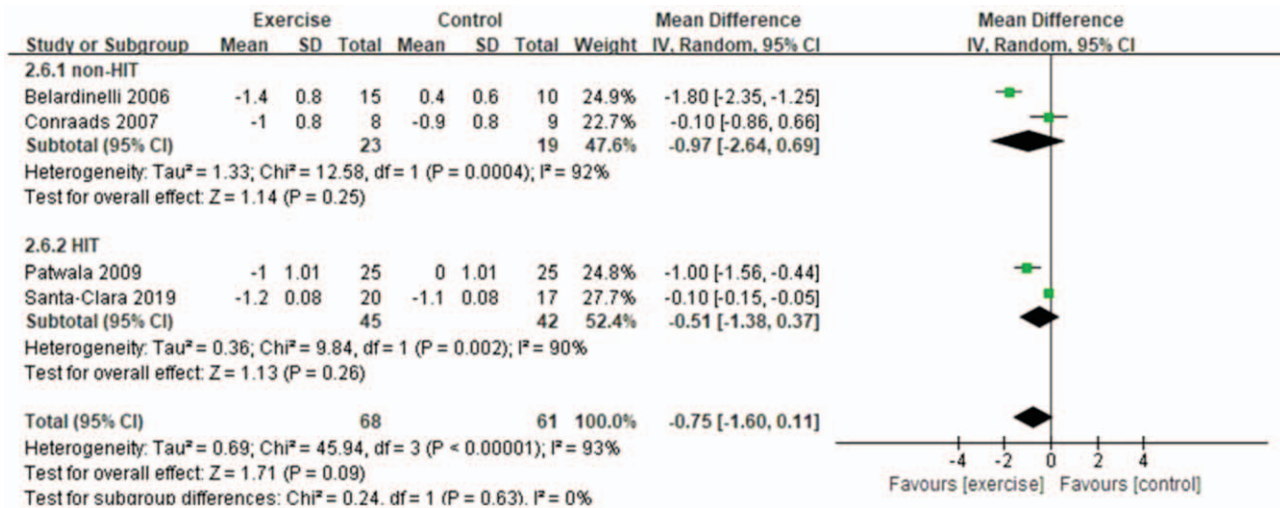


Figure 7. Impact of non-HIT and HIT on the change of NYHA class in CHF patients with CRT. CHF = chronic heart failure, CRT = cardiac resynchronization therapy, HIT = high intensity training, non-HIT = light to moderate intensity training, NYHA = New York Heart Association.

demonstrated a statistically significant improvement versus control groups.

It is generally recognized that CHF is characterized by sympathetic hyperactivity, which initially helps to stabilize individuals with contractile dysfunction. But with time, neurohumoral excitation leads to chronic vasoconstriction and it may be an important instigator of skeletal myopathy. Coats and his colleagues believe that skeletal myopathy plays a key role in the exercise intolerance and prognosis of CHF patients.^[30] Studies have shown that ET can reduce the sympathetic activation of CHF patients by regulating arterial baroreceptors, cardiopulmonary receptors, and chemoreceptors, thereby improving peripheral blood flow and skeletal myopathy, and ultimately, improving the exercise capacity and quality of life of CHF patients.^[31]

In our analyses, the peak VO_2 of participants in the ET group was averagely improved by 2.73 ml/kg/minute. This is consistent with the mean increment of about 16.5% in heart failure patients with aerobic ET reported by Smart et al containing 40 studies.^[32] And the result has clearly exceeded the threshold of clinically meaningful change of peak VO_2 (1 ml/kg/minute or 10%).^[33] The above contents indicate that ET is safe and effective in improving the exercise capacity of CHF patients with CRT, and this is important since the primary symptom of heart failure with reduced ejection fraction (HFrEF) patients is exercise intolerance.

Many literatures have reported the effects of ET on cardiac function in CHF patients. Though, data on whether ET can improve LVEF is still conflicting.^[34] A meta-analysis of 14 studies indicated that aerobic ET had its ability to reverse ventricular remodeling in HFrEF patients and significantly increased LVEF by 2.59%.^[15] And our analyses showed that the LVEF of participants in the non-HIT group was significantly increased by 4.97%. The probable reasons for the improvement were that, firstly, CRT has been shown to reverse ventricular remodeling and improve systolic and diastolic function.^[35] Secondly, perhaps attributed to the decrease of vasoconstrictive neurohormones or the reduction in circulatory overload. As a result, an increase in LVEF can reduce all-cause mortality in heart failure patients.^[36]

Another finding in our analysis was that participants in the non-HIT group compared to the control group had a statistically significant improvement in HRQoL, with an average decrease of 19.96 in MLHFQ. In addition, 2 other studies using NHP and the Portuguese version of the HeartQoL also showed a statistical improvement of HRQoL in the ET group. It was worth noting that Ostman et al, exploring the effects of exercise intensity on QoL in heart failure patients, presented that as exercise intensity increased, the QoL of patients elevated.^[37] And Ismail et al also reported that with exercise intensity enhanced, exercise adherence was higher and the extent of improvement in cardiorespiratory fitness increased in heart failure patients.^[38] While our current evidence did not spot a statistical difference in these above endpoints between the HIT and control groups. The possible reasons we analyzed came after, first, the rate of lost to follow-up was high. Santa-Clara et al stated the lost rate in the HIT group was almost 41%, and the main cause was that most participants (92.9%) failed to complete the exercise protocol.^[26] Although in most European countries, the proportion of patients participating in post-hospital rehabilitation is less than 50%, this may still not to be underestimated. Second, the mass of participants included was small, which might come out bias. For example, in the study of Spee et al, all women were randomly assigned to the control group, and the number of DCM in the control group was greater than that of patients with ischemic cardiomyopathy.^[27] Since the former responds better to CRT. Finally, extensive intensity, fatigue and exhaustion, and exercise intolerance made it hard for advanced heart failure patients to carry out. Gayda et al suggested that for cardiac disease patients with less fit and/or high risk, it is recommended to start from continuous aerobic exercise training and gradually increase intensity to the exercise program.^[39] In spite of that, participants in the HIT group performed well on maximal workload. Spee et al proposed that this was owing to the HIT increased the performance or efficiency of anaerobic exercise.^[27] In summary, it should be carefully explained that the HIT mentioned in this review did not provide a statistically significant benefit to CHF patients after CRT implantation and more evidence is demanded to determine the impact of the HIT on CHF patients with CRT.

4.1. Strengths and limitations

We believe this is by far the most comprehensive systematic review of ET program for CHF patients after CRT implantation, but there are still several limitations. First of all, the number of included subjects was small, which drove the results more susceptible to the characteristics of involved participants and diminished the representativeness. Besides, as the small number of participants in general, the mortality and hospitalization were difficult to estimate. At present, it could only be roughly judged by qualitative analysis, and a large-scale study involving more participants is required. In the second place, the exercise program of different studies was dissimilar. Even though the subgroup analysis was carried out, giving the limited eligible studies, the conclusion needs to be further employed with caution. More clinical research specific to a certain exercise modality is needed to draw a definitive conclusion accordingly.

5. Summary

Compared with no exercise or routine care control, the peak VO₂, LVEF, and HRQoL in CHF patients with CRT were statistically improved with light to moderate intensity training, but there seemed no difference of above endpoints in the HIT group during short-term follow-up (up to 6 months). Regardless of the exercise intensity, our analysis also found that compared with control, the maximal workload and exercise duration of participants in the ET group had a significant improvement. In addition, the mortality and hospitalization did not increase both in the HIT and non-HIT groups. However, limited by the number of participants in this present study, it is necessary for a large-sample multicenter trial to further evaluate the clinical benefits of different exercise modalities to CHF patients after CRT implantation. Supplemental Digital Content, <http://links.lww.com/MD/F970>.

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