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Resistance exercise enhances oxygen uptake without worsening cardiac function in patients with systolic heart failure: a systematic review and meta-analysis

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Abstract Recent literature suggests that resistance training (RT) improves peak oxygen uptake ($\dot{V}O_2$ peak), similarly to aerobic exercise (AE) in patients with heart failure (HF), but its effect on cardiac remodeling is controversial. Thus, we examined the effects of RT and AE on $\dot{V}O_2$ peak and cardiac remodeling in patients with heart failure (HF) via a systematic review and meta-analysis. MEDLINE, EMBASE, Cochrane Library and CINAHL, AMEDEO and PEDro databases search were extracted study characteristics, exercise type, and ventricular outcomes. The main outcomes were $\dot{V}O_2$ peak (ml kg^{-1} min^{-1}), LVEF (%) and LVEDV (mL). Fifty-nine RCTs were included. RT produced a greater increase in $\dot{V}O_2$ peak (3.57 ml kg^{-1} min^{-1}, $P < 0.00001$, $I^2 = 0\%$) compared to AE (2.63 ml kg^{-1} min^{-1}, $P < 0.00001$, $I^2 = 58\%$) while combined RT and AE produced a 2.48 ml kg^{-1} min^{-1} increase in $\dot{V}O_2$; $I^2 = 69\%$) compared to control group. Comparison among the three forms of exercise revealed similar effects on $\dot{V}O_2$ peak ($P = 0.84$ and 1.00, respectively; $I^2 = 0\%$). AE was associated with a greater gain in LVEF (3.15%; $P < 0.00001$, $I^2 = 17\%$) compared to RT alone or combined exercise which produced similar gains compared to control groups. Subgroup analysis revealed that AE reduced LVEDV (− 10.21 ml; $P = 0.007$, $I^2 = 0\%$), while RT and combined RT and AE had no effect on LVEDV compared with control participants. RT results in a greater gain in $\dot{V}O_2$ peak, and induces no deleterious effects on cardiac function in HF patients.

Keywords Ventricular remodeling · Performance · Exercise capacity · Heart failure

Abbreviations

HR	Heart rate
HFrEF	Heart failure with reduced ejection fraction
LVEDV	Left ventricular end diastolic volume
LVEF	Left ventricular ejection fraction
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
MR	Maximal repetition
RT	Resistance training
AE	Aerobic exercise
$\dot{V}O_{2\ peak}$	Peak oxygen uptake

Introduction

The structural and functional consequences of heart failure (HF) appear to trigger several compensatory mechanisms, such as gene expression, sympathetic stimulation, neurohumoral activity [1, 2], and exercise intolerance. HF mortality rates remain high, regardless of current therapeutic management strategies. However, HF patients with better exercise tolerance and higher oxygen uptake have better survival [3, 4].

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Studies have showed that exercise is a safe and effective intervention to improve oxygen uptake ($\dot{V}O_2$ peak) in patients heart failure with reduced ejection fraction (HFrEF) [5–7]. This response is linked to favorable changes in cardiovascular and skeletal muscle function [8]. In fact, different studies have reported the effectiveness of exercise on clinical consequences of left ventricle remodeling and exercise capacity, which may impact HFrEF prognosis [9–14]. This benefit has been confirmed only with aerobic exercise, through attenuation of sympathovagal dysfunction leading to an improved peripheral vasodilation [13, 15, 16]. Moreover, a previous meta-analysis by Haykowsky et al. that included only HFrEF patients [15] reported that combined aerobic exercise (AE) and resistance training (RT) improved upper extremity muscle strength compared to AE alone while the change in $\dot{V}O_2$ peak and lower extremity strength were not different between AE, combined AE and RT, and RT alone. Also, the authors reported that detrimental effects of AE on ventricular remodeling do not occur when combined with RT due to excessive increase in left ventricular afterload caused by resistance exercise [15]

In contrast, recent studies [8, 12, 17] have shown that the RT produces similar effects compared to combined AE and RT and AE alone without impairing the left ventricular ejection fraction. However, the literature is quite divergent on its effects. Furthermore, previous studies nor meta-analyses have not performed statistical comparisons between combined AE and RT versus AE and RT versus AE. In addition, it is unclear what effect RT might have on cardiac remodeling. [12, 18–20]. To clarify this question, we conducted a comprehensive overview of the effects from combined AE and RT or RT alone on cardiac remodeling and functional capacity in patients with systolic HF. We hypothesized that RT can improve functional capacity without causing deleterious effects on cardiac function in patients with HF.

Methods

Search strategy

We conducted a systematic review and meta-analysis in compliance with the recommendations and criteria described in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and Cochrane Handbook [21]. The protocol was registered in the PROSPERO database (www.crd.york.ac.uk/prospero/) under number: CRD42014013857.

Sources of data

Potential studies were identified via a comprehensive strategy. The systematic review was performed in the following databases: *MEDLINE* (Ovid) (1950 to March 2016); *EMBASE* (1974 to 2016), *The Cochrane* and *CINAHL* (1981 to 2016); Amedeo (1997 to March 2016) and PEDro (1929 to March 2016). The search strategy involved the crosschecking of keywords selected based on the Medical Subjects Headings (Mesh) – United States National Library of Medicine and free terms for key words (intervention + population), with filters to limit the search to clinical trials (Phases I–IV), controlled clinical trials, multicenter studies, randomized controlled trials, pragmatic clinical trials and systematic reviews. There was no language restriction. The following keywords were used for (i) intervention: "Resistance exercise"*[Mesh] OR* "Muscle Contraction"*[Mesh] OR* "Muscle Strength"*[Mesh] OR* "Muscle Strength Dynamometer"*[Mesh] OR* "Exercise"*[Mesh] OR* "Exercise Therapy"*[Mesh] OR* "Exercise Tolerance"*[Mesh] OR* "Exercise Test"*[Mesh] OR* "Physical Education and Training" *[Mesh] OR* "Physical and Rehabilitation Medicine" [*Mesh] OR* "Physical Fitness" [*Mesh] OR* "Physical Exertion" [*Mesh] OR* "Physical Endurance" [*Mesh*]; (ii) outcomes: "Ventricular Remodeling"*[Mesh]OR* "Myocardium"*[Mesh] OR* "Myocardial Contraction"*[Mesh] OR* "Atrial Remodeling"*[Mesh] OR* "Myocytes, Cardiac"*[Mesh] OR* "Exercise Tolerance"*[Mesh]*; and (iii) Population studied: "Cardiomyopathies" *[Mesh] OR* "Heart Failure" *[Mesh] OR* "Cardiomegaly"*[Mesh]*. The studies were selected in accordance to Cochrane handbook [21]. The authors initially assessed the title and abstract (type of study design, description of population and information on interventions) for eligibility. After the selection of potentially relevant studies, the full-text versions were analyzed for methodological quality by two researchers independently and disagreement between reviewers was resolved by discussion or arbitration by the other researcher. The degree of the disagreement was measured by Kappa statistic.

Quality (risk of bias) and publication bias assessment

Two researchers evaluated study quality and risk of publication bias independently, using the PEDro scale [22] based on the Delphi list developed by Verhagen et al. [23]. This scale includes the following items to be evaluated: eligibility criteria, randomization, allocation concealment, similarity in baseline data, blinding of subjects, blinding of therapists, blinding of evaluators, adequate follow up, intention-to-treat analysis, statistical analysis among groups and the use of measures.

Types of studies and participants

The following criteria were adopted for the selection of the studies: Randomized Clinical Trials (RCTs) with or without a cross-over strategy; interventions involving physical exercises based on The Cochrane Review Handbook [21]; and an

experimental group submitted to AE, RT, and combined AE and RT, with control group or between intervention group. The population consisted of adult individuals with a diagnosis of systolic heart failure (based on clinical findings and objective indices, such as ejection fraction < 45% and functional classes I to IV) without age limitations. Studies with specific populations such as exclusively elderly or young subjects were excluded.

Types of interventions and outcomes

We considered RT alone, AE alone or a combination of both AE and RT performed at hospital, outpatient, and home-based settings. We considered interventions with the following parameters: (1) frequency: 2–4 days per week; (2) duration: at least 8–26 weeks; (3) intensity: 50–90% of maximum heart rate (HR_{max}) or 50–80% of $\dot{V}O_2$ for aerobic exercise and 40–80% of one maximum repetition (1-MR) for resistance exercise. The clinical outcomes of the studies must have evaluated at least one of the following measures: peak oxygen uptake ($\dot{V}O_2$ peak, ml kg^{-1} min^{-1}), left ventricular ejection fraction (LVEF, %) and left ventricular end diastolic volume (LVEDV, mL).

Data extraction

All relevant data regarding the inclusion criteria [(type of study, population, interventions (including type of exercise, intensity, frequency, duration and modality), comparison and outcomes], risk of bias (randomization, blinding and presence of a control group) and results were extracted from all selected studies. A single researcher performed the extraction procedure and a second researcher scrutinized it.

Data analyses

Relative changes in $\dot{V}O_2$ and absolute changes in LVEF and LVEVD were reported as differences between arithmetic means before and after interventions. Data from intention-to-treat analyses were entered whenever available in included RCTs. Pooled-effect estimates were obtained by comparing the least squares mean percentage change from base line to the end of the study for each group, and were expressed as the weighted mean difference (WMD) between groups. Calculations were performed using a random-effects model. Tests for subgroup differences based on random-effects models may be regarded as preferable to those based on fixed-effect models, due to the high risk of false-positive results when comparing subgroups in a fixed-effect model [21]. Four comparisons were made with each group being compared with a no intervention (control) group: AE, RT, combined AE and RT, and control. An α value = .05 was considered statistically significant.

Publication bias was assessed using a contour-enhanced funnel plot of each trial's effect size against the standard error. Funnel plot asymmetry was evaluated by Begg and Egger tests. Statistical heterogeneity of the treatment effect among studies was assessed using Cochran Q test, a threshold P value < 0.05 was considered statistically significant, and the inconsistency I^2 test in which values greater than 50% were considered indicative of high heterogeneity [21]. The heterogeneity between included studies was explored. First, we reanalyzed the meta-analyses removing each study at a time to determine if a particular study was explaining substantial heterogeneity. Second, we performed sensitivity analyses to evaluate subgroups of studies most likely to yield valid estimates of the intervention based on preexistent relevant clinical information. All analyses were conducted using Review Manager Version 5.0.

Results

Selection and evaluation of studies

The initial search identified 4.919 studies on AE and RT (either alone or in combination with AE) involving patients with systolic HF. Two duplicate studies were removed yielding a total of 4917 studies. After title and abstract analysis, we excluded 4.827 studies which were ineligible based on inclusion criteria (Fig. 1). Thirty-one studies were not eligible after entire text analysis: 15 studies regarding RT alone or combined AE and RT [24–38], and 16 studies regarding AE [39–54] were excluded to (a) absence of comparative group, (b) absence of analyzed outcomes, (c) protocol not in accordance to the inclusion criteria, (d) absence of data outcome in mean and standard deviation, (e) cross-sectional studies, and (f) HF with preserved ejection fraction (Table 1).

The present systematic review and meta-analysis included a total of 59 studies: 29 involving RT alone and/or combined AE and RT (Table 2) and 32 involving AE (Table 3). One study [12] was included in all comparisons, and another study [97] was included in AE and combined AE and RT comparisons. In one study [97], the data was described in median and interquartile range and not in mean and standard deviation. Thus, we converted the median and interquartile range to obtain a good estimate of the mean and standard deviation of the sample using the following methodology: Through the median values and interquartile ranges the percentile values were estimated from 5 to 95%, for every 5%, by proportional estimates. Using the estimated values, fourth order polynomial equations were calculated with good linearity (r^2 > 0.9). The four polynomial equations (one for each sample) were obtained according to each sample size, as previously described. Finally, with the

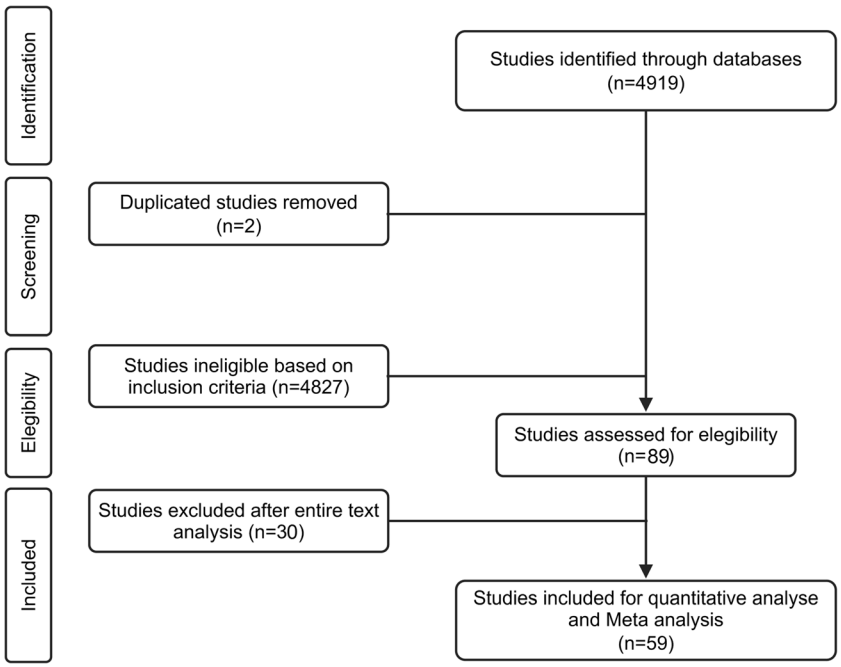


Fig. 1 Study flow diagram

projection of the individual those values average and the standard deviation values were calculated [105–107].

Studies included in systematic review

Publication dates of the included studies ranged from 1992 to 2015, involving a total of 5.046 patients with 3.939 (78.1%) being male having a mean age of 58.20 ± 7.99 years. The HF patients were clinically stable, with New York Heart Association functional classes between I and IV. LVEF range was from 20 to 45%. Mean training frequency for RT alone and combined AE and RT was 3.00 ± 0.49 days per week, with a mean duration of 49.80 ± 16.70 min per session and mean protocol duration of 17.80 ± 4.90 weeks. The mean frequency of AE was 4.00 ± 1.76 times per week, with a mean duration of 44.90 ± 14.90 min per session and mean protocol duration of 17.80 ± 8.60 weeks. The intensity of AE ranged from 50 to 80% of $\dot{V}O_2$, 40–90% of HR_{max} or 40–80% of heart rate recovery (HRR). The intensity of resistance exercise ranged from 30 to 90% of 1MR (Table 2). Heterogeneity among the studies was low ($I^2 < 50\%$), except for comparative analyses between AE and combined AE and RT with a control group (I^2 = 58% and 69%, respectively) in $\dot{V}O_2$ peak outcome. None of the studies reported adverse effects during the study protocols of RT, AE, or combined AE and RT.

Combined AE and RT was compared with AE in eight studies [8, 11, 12, 17, 67, 71, 72, 74]; control group in 14 studies [12, 57–59, 61–65, 69, 73, 75–77]; and RT alone in one study [12]. RT alone was compared with AE in three studies [12, 68, 70]; control group in eight [12, 18–20, 56, 60, 66, 70]. Thirty-two studies compared AE alone to a control group, [8–10, 12, 55, 78–104]. The analysis of quality using the PEDro scale demonstrated scores ranging from 5 to 8 points for both RT alone, combined AE and RT, as well as AE alone. The level of agreement between the reviewers, which was calculated using the Kappa coefficient, was 0.95 (95% CI 0.88 to 1.0).

Exercise and peak oxygen consumption ($\dot{V}O_2$ peak)

In overall, exercise was associated with a significant improvement of the $\dot{V}O_2$ peak when data of all studies was pooled (46 studies, n = 4.296 patients, weighted mean difference [WMD] = 2.70 ml kg^{-1} min^{-1}, 95% CI 2.11 to 3.28 ml kg^{-1} min^{-1}, I^2 = 65%) (Fig. 2a). In the isolated analysis, both RT, AE and Combined AE and RT was associated with gain in $\dot{V}O_2$ peak (RT: 5 studies, n = 124 patients, WMD = 3.57 ml kg^{-1} min^{-1}, 95% CI 2.45 to 4.68 ml kg^{-1} min^{-1}, I^2 = 0%; AE:28 studies, n = 3.584 patients, WMD = 2.63 ml kg^{-1} min^{-1}, 95% CI 1.96 to 3.29 ml kg^{-1} min^{-1}, I^2 = 2%; combined AE and RT (13 studies, n = 588 patients, WMD = 2.48 ml kg^{-1} min^{-1}, 95% CI 0.88 to 4.09 ml kg^{-1} min^{-1}, I^2 = 69%). The results of the analysis were inconclusive for comparisons between: Combined AE and RT versus AE (08 studies, n = 283 patients, WMD = 0.69 ml kg^{-1} min^{-1}, 95% CI − 0.87 to 2.25 ml kg^{-1} min^{-1}, I^2 = 0%) and RT versus AE (03 studies, n = 75 patients, WMD = 0.12 ml kg^{-1} min^{-1}, 95% CI − 1.22 to 1.45 ml kg^{-1} min^{-1}, I^2 = 0%) (Fig. 2b). There was only one trial comparing combined AE and RT versus RT alone (n = 30, WMD = − 0.60 ml kg^{-1} min^{-1}, 95% CI − 3.82 to 2.62 ml kg^{-1} min^{-1}).

Table 1 Reasons for exclusion of trials

Study [ref], year.	Reason for exclusion
Maiorana et al. 2000 [34]	Absence of comparative group
Larsen et al. 2001 [40]	
Miche et al. 2008 [35]	
Karapolat et al. 2009 [41]	
Savage et al. 2011 [38]	
Aslanger et al. 2015 [30]	
Hambrecht et al. 1998 [42]	Outcomes analyzed not shown
Myers et al. 2002 [55]	
Jankowska et al. 2007 [32]	
Gary et al. 2011 [29]	
Gary et al. 2012 [31]	
Keteyian et al. 2012 [43]	
Cowie et al. 2012 [44]	
Mentz et al. 2013 [45]	
Ahmad et al. 2014 [46]	
Owen et al. 2000 [47]	
Coats et al. 1992 [39]	Protocol not in accordance
Tyni-Lenne et al. 1997 [38]	
Besson et al. 2013 [48]	
Koufaki et al. 2014 [49]	
Delagardelle et al. 2002 [27]	Mean and standard deviation data not shown
Kemps et al. 2010 [33]	
Nishi et al. 2011 [50]	
Caminiti et al. 2011 [25]	
Belardinelli et al. 2012 [51]	
Taylor et al. 1999 [52]	Acute effects of resistance exercise
Cheetham et al. 2002 [26]	
Kitzman et al. 2010 [54]	Heart failure without systolic dysfunction
Edelmann et al. 2011 [28]	
Smart et al. 2012 [8]	
Kitzman et al. 2013 [53]	

Exercise and left ventricular ejection fraction (LVEF)

When data of all studies comparing exercise versus control group was pooled, the exercise demonstrated favorable effects on LVEF (32 studies, $n = 1.373$ patients, WMD = 2.33%, 95% CI 1.20 to 3.47%, $I^2 = 26\%$) (Fig. 3a). However, LVEF did not improve with the isolated analysis of RT (04 studies, $n = 86$ patients, WMD = 1.91%, 95% CI − 3.71 to 7.53%, $I^2 = 23\%$) and combined with AE (11 studies, $n = 468$ patients, WMD = 0.02%, 95% CI − 1.47 to 1.52%, $I^2 = 0\%$). The improvement of LVEF occurred only in the analysis of AE (17 studies, $n = 819$ patients, WMD = 3.15%, 95% CI 1.87 to 4.44%, $I^2 = 17\%$). The studies comparing combined AE and RT versus AE were also inconclusive (03 studies, $n = 78$ patients, WMD = 0.06%, 95% CI − 4.14 to 4.27%, $I^2 = 0\%$) (Fig. 3b). Only one study compared RT isolated with AE ($n = 20$, WMD = − 3.00, 95% CI − 9.92 to 3.92%) and combined AE with RT ($N = 30$ patients, WMD = − 3.00, 95% CI − 4.65 to 10.65%).

Exercise and left ventricular end diastolic volume (LVEDV)

AE produced an improvement in LVEDV (08 studies, $n = 478$ patients, WMD = − 10.21 mL 95% CI − 17.64 to 2.77 mL) (Fig. 4). No improvement was found in the analyses of the combined AE and RT (04 studies, $n = 239$ patients, WMD = 1.98 mL 95% CI − 3.14 to 7.09 mL) and RT alone (02 studies, $n = 46$ patients, WMD = − 7.93 mL 95% CI − 49.82 to 33.97 mL) versus control. Overall, exercise was not associated with a significant improvement in LVEDV when data from all trials were pooled (14 studies, $n = 763$ patients, WMD = − 2.42 mL 95% CI − 6.88 to 2.04 mL). One trial comparing combined AE and RT versus RT alone had inconclusive results ($n = 30$, WMD = − 7.00 mL. 95% CI − 67.28 to 53.28 mL) as well as the comparison between RT alone versus AE ($n = 30$, WMD = 1.00 mL, 95% CI − 49.92 to 51.92 mL).

Discussion

The present meta-analysis supports current and robust evidence that RT in HF patients administered alone or in combination with AE may be able to offer benefits to the cardiopulmonary capacity without causing deleterious effects on cardiac function. Moreover, even with the inclusion of more recent studies after the study by Haykowsky et al RT—alone or combined—had no detrimental influence on ventricular remodeling variables. These findings add relevant information to previously published meta-analysis on this topic [15].

In this study, we reanalyzed more recent studies that assessed the effects of AE on three clinical outcomes of interest ($\dot{V}O_2$ peak, LVEF and LVEDV), to compare with those obtained with RT. We found that AE produced benefits in all three clinical outcomes. Our results are in agreement with previous meta-analysis for the outcomes of ventricular remodeling [16] and $\dot{V}O_2$ peak [108]. The magnitude of gain in the $\dot{V}O_2$ peak may be related to higher training intensity, with greater gains after vigorous intensity training programs, without a significant increase in the risks of death, cardiac events and hospitalizations [109]. Despite of previous meta-analysis [110] that demonstrated superior results of the interval training on cardiac remodeling in comparison to continuous training, recent randomized multicenter trial do not demonstrated superior results of the interval training over continuous training in

Table 2 Description of studies on resistance isolated and combined exercise included in systematic review and meta-analysis

Study [ref], year	Study, sample	Sample size (*n*)	Age (years) (mean + SD)	Outcomes	Intervention description	Frequency (days/week)	Session duration (min)	Program duration (week)	PEDro score
Koch et al. [19] 1992	HF FC I-III/LVEF < 40%	ST 12 CG 13 CG 7	56 ± 11 54 ± 10 75 ± 5	LVEF	40 sessions on KOCH Bench - small number of muscle groups	3	90	12	5
Tynni-Lenné et al. [56] 2001	HF FC II-III/LVEF ≤ 40%	ST 16 CG 08	63 ± 9 62 ± 11	$\dot{V}O_2$ peak	Borg < 12 (central exertion) and 13 to 16 (muscle exertion) (Therabands in six different colors)	3	60	8	5
McKelvie et al. [57] 2002	HF FC I-III/LVEF < 40%	CT 90 CG 91	64.8 ± 1.1 66.1 ± 0.9	LVEF + LVEDV	AT: 60%–70% HRmax (cycle + treadmill + arm ergometry) + ST: 40–60% 1RM	3	30	12 (superv) 36 (home)	7
Stolen et al. [58] 2003	HF FC I-III/LVEF < 40%	CT 9 CG 7	55 ± 8 55 ± 8	$\dot{V}O_2$ peak + LVEF	AT: 50–70% $\dot{V}O_{2\ peak}$ (cycle) + ST (trunk + upper and lower body) Borg + HR	3 (AT) 2 (ST)	45	20	5
Roveda et al. [59] 2003	HF FC II-III/LVEF ≤ 40%	CT 7 CG 9	53 ± 9 46 ± 5	$\dot{V}O_2$ peak + LVEF	AT: Up10% below RCP (cycle) + ST: Local strength exercise (sit-up + push-up + pull-up)	3	60	16	6
Selig et al. [60] 2004	HF FC II-IV/LVEF < 40%	CT 14 CG 19	65 ± 13 64 ± 9	$\dot{V}O_2$ peak	Circuit training with aerobic and strength exercises (multi-station system and cycle) - Moderate intensity	3	12	12	5
Sabelis et al. [61] 2004	HF FC II-III/LVEF < 40%	CT 16 CG 13	59.6 ± 8.3 60 ± 8	$\dot{V}O_2$ peak + LVEF	AT: 70% HRmax (endurance exercise) + ST 50% maximum short-term exercise capacity (major muscle groups)	2 (superv) 2 (home)	60 (superv) 11 (home)	26	5
Senden et al. [62] 2005	HF FC II-III/LVEF < 35%	CT 25 CG 36	59.8 ± 9.3 59.8 ± 9.3	$\dot{V}O_2$ peak	Home: Strength for major muscle groups + stationary run/Superv: Interval training (50% maximal performance SRT) + Strength training (70% HRpeak)	2 (superv) 2 (home)	> 11	26	4
Levinger et al. [19] 2005	HF FC II-IV/LVEF < 40%	ST 8 CG 7	57.3 ± 11 56.7 ± 10	LVEF	ST: 40–60% 1RM (9 exercises on major muscle groups)	3	50	8	5
de Mello Franco et al. [63] 2006	HF FC II-III/LVEF < 40%	CT 17 CG 12	56 ± 2,9 52 ± 2,2	$\dot{V}O_2$ peak + LVEF	Endurance (Cycle – 20 to 40 min) + local Strength exercises (10 min) to 10% below RPC.	3	60	16	5
Jonsdottir et al. [64] 2006	HF FC II-III/LVEF < 45%	CT 21 CG 22	68 ± 6.6 69 ± 5.3	$\dot{V}O_2$ peak + LVEF + LVEDV	AT: 50% peak work (cycle) + ST: 20%–40% 1RM (circuit training - free weight and elastic band)	2	50	20	4
Dracup et al. [65] 2007	HF FC II-IV/LVEF < 40%	CT 87 CG 86	53,3 ± 12,7 54,6 ± 12,5	$\dot{V}O_2$ peak	Walking (40–60% FCmax) and Strength for major muscle groups (80% 1RM)	4	60	12	6
Williams et al. [66] 2007	HF FC II-III/LVEF < 40%	ST 07 CG 06	67 ± 9 64 ± 4	$\dot{V}O_2$ peak	Intensity graduated up to 5 bpm below HRmax (multistation resistance system + arm and leg cycle)	3	Not described	12	6
Feiereisen et al. [12] 2007		ST 15 CT 15	57.9 ± 5.8 60.6 ± 5.6			3	40	13	5

Table 2 (continued)

Study [ref], year		Study, sample	Sample size (*n*)	Age (years) (mean + SD)	Outcomes	Intervention description	Frequency (days/week)	Session duration (min)	Program duration (week)	PEDro score
		HF FC II-III/LVEF < 35%	AT 15 CG 15	59.4 ± 6.5 55.5 ± 7.5	$\dot{V}O_2$ peak + LVEF + LVEDV	AT: 60–75% $\dot{V}O_{2\ peak}$ (cycle + treadmill) / ST: 60%–70% 1RM (trunk + upper and lower body)				
Beckers et al. [11]	2008	HF FC II-III/LVEF < 40%	CT 28 AT 30	58 ± 11 59 ± 11	$\dot{V}O_2$ peak	CT: 90%HRmax (circuit training) + ST: 50–60% 1RM (four major muscle groups)	3	60	24	5
Palevo et al. [20]	2009	HF FC I-III/LVEF < 40%	ST 10 CG 06	60 ± 12 65 ± 13	LVEF + LVEDV	60% 1RM (free weights and/or machines for major muscle groups)	3	30	8	6
Mandic et al. [8]	2009	HF FC I-III/LVEF < 40%	CT 10 AT 8 CG 13	59 ± 11 63 ± 11 62 ± 13	$\dot{V}O_2$ peak + LVEF	CT: 50–70% HRR + Borg 11–14 (cycle-15 min + treadmill-15 min) + ST: 50–70% 1RM (trunk + upper and lower body)	3	30	12	7
Bouchla et al. [67]	2011	HF I-III/LCEF < 40%	AT 10 CT 10	50.5 ± 11 56.7 ± 7.2	$\dot{V}O_2$ peak	AT: 50% peak workload interval Training (30 s exerc and 60 s rest) / CT: AT + ST: 4 muscle groups 55–65% 1RM	3	AT: 40 CT: 60	12	5
Jakovljevic et al. [68]	2010	HF FC I-II/LVEF < 40%	ST 10 AT 11	63 ± 10 65 ± 12	$\dot{V}O_2$ peak	AT: 60–80% $\dot{V}O_{2\ peak}$ + Borg (circuit training) + ST (circuit training - major muscle groups)	5 (4 in home)	30	12	5
Santos et al. [69]	2010	HF LVEF < 45%	CT 13 CG 10	53.1 ± 12.7 59.4 ± 12.2	LVEF + LVEDV	AT: 10% below RCP (cycle) / ST: 10 min of local strengthening exercises	3	40	16	5
Maiorana et al. [70]	2011	HF FC I-III/LVEF < 40%	ST 12 AT 12 CG 12	58.8 ± 3.5 61.3 ± 2.8 64.4 ± 2.4	$\dot{V}O_2$ peak	AT: 50–70% $\dot{V}O_{2\ peak}$ (cycle + treadmill)/ ST: 50%–70% 1RM	3	46.5	12	5
Anagnoustakou et al. [71]	2011	HF FC I-III/LVEF < 45%	CT 14 AT 14	54 ± 10 52 ± 11	$\dot{V}O_2$ peak	AT: 50% workload of SRT (cycle interval training) + ST: 55–65% 2RM (major muscle groups)	3	40	12	4
Laoutaris et al. [17]	2013	HF FC II-III/LVEF < 40%	CT 13 AT 14	57.1 ± 11 58.6 ± 8	$\dot{V}O_2$ peak + LVEF	CT: 70%–80% HRmax (cycle) ST: 50% 1RM + RMT (60% SPImax)	3	65	12	6
Keast et al. [72]	2013	HF FC II-III/LVEF < 35%	CT 27 AT 27	62.8 ± 11 62.1 ± 12	$\dot{V}O_2$ peak	CT: Hand-held weights or therabands + Walking / AT: Nordic Walking. 60–75% HRR and Borg 3–5	2	75	12	6
Antunes-Correa et al. [73]	2014	HF FC II-III/LVEF < 40%	CT 17 CG 17	56 ± 2 54 ± 2	$\dot{V}O_2$ peak + LVEF	CT: 60–72% $\dot{V}O_{2\ peak}$ (cycle) / ST: 10 min of local strengthening exercises	3	60	16	5
Georgantas et al. [74]	2014	HF I-III/LVEF < 45%	CT 22 AT 20	55 ± 11 53 ± 11	$\dot{V}O_2$ peak	AT: AIT (Cycle to 50% peak work SRT – 30s exec and 60s rest) CT: AIT + Strength exercise for major muscle groups	3	12	40	5
de Meirelles et al. [75]	2014	HF FC II-III/LVEF < 35%	CT 15 CG 15	54 ± 3 55 ± 2	$\dot{V}O_2$ peak	CT: 5%–15% above VT (30 min treadmill) / ST: 8 to 10 exercises for the major muscle groups	3	90	24	6

Table 2 (continued)

Study [ref], year	Study, sample	Sample size (*n*)	Age (years) (mean + SD)	Outcomes	Intervention description	Frequency (days/week)	Session duration (min)	Program duration (week)	PEDro score
Chrysohoou et al. 2015 [76]	HF I-III/LVEF < 35%	CT 33 CG 39	63 ± 9 53 ± 11	$\dot{V}O_2$ peak	CT: 80–100% peak WR interval training (30 s exerc / 30 s rest) / ST: 4 exercises at 30–90% 1RM	3	45	12	6
Groehs et al. [77] 2015	HF FC II-III/LVEF < 40%	CT 13 CG 13	57 ± 3 49 ± 3	$\dot{V}O_2$ peak + LVEF + LVEDV	CT: 08–10% below RCP (cycle) / ST: 10 min of local strengthening exercises	3	60	16	6

Legends: HF, heart failure; FC, functional class; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end diastolic volume; AT, aerobic training; ST, strength training; CT, combined training; CG, control group; AIT, aerobic interval training; 1RM, one maximum repetition; HRmax, maximum heart rate; HRR, heart rate reserve; SRT, steep ramp test; RMT, respiratory muscle training; RPC, respiratory point compensation; VT, ventilatory threshold; SPImax, sustained maximum inspiratory pressure; WR, work rate

this outcome [7]. Additionally, superiority was not confirmed on$\dot{V}O_2$ peak in both modalities of training. Furthermore, in patients with preserved systolic function HF published by Dieberg et al. demonstrated similar results to ours on the effects of AE upon $\dot{V}O_2$ peak [111]. Also, Lavie et al. in a recent review study reported similar effects of $\dot{V}O_2$ peak in HF patients with preserved and reduced ejection fraction, with improvements in $\dot{V}O_2$ peak of >16% after aerobic exercise [112].

Effects of resistance training alone

Exercise intolerance in patients with HF had been related to abnormalities in skeletal muscle as well as cardiac dysfunction itself [112]. The increase in muscle mass and strength provided by RT can positively influence $\dot{V}O_2$ peak [12]. Muscle mass emerged as a clinically relevant variable for patients with HF since it was confirmed as an independent predictor for mortality [113]. In the present study, both RT and AT studies were able to produce favorable results in cardiopulmonary capacity with significant increase in peak $\dot{V}O_2$ compared to a control group.

RT induces a decrease in neuro-hormonal activity which may directly contribute to an improve~~d~~ on exercise capacity from patients with HF [73, 114]. The rationale for RT prescription in HFrEF patients is based on a favorable correlation between the muscle function increase and the exercise capacity improvement [94]. Additionally, the RT effects on attenuation of skeletal muscle atrophy support the recommendation to perform this type of exercise. Other study also demonstrates its relation between the increase in muscle mass and muscle oxygen consumption by an increase from blood oxygen extraction during exercise leading to an increase in total body oxygen consumption [8].

Regarding to the AT method, the increase of the exercise capacity has been related to changes in cardiovascular structure and function [96], as well as in the muscle metabolism [85] and strength [111]. Thus, AT is an important method to improve exercise capacity and prognosis in HFrEF patients. The peripheral muscular adaptations have been responsible to the significant improvement in $\dot{V}O_{2\ peak}$ and VE/VCO2 slope after a moderate-intensity AT in these patients, as well as the improvement of oxygen consumption efficiency slope, a predictor of cardiorespiratory performance in HFrEF [70]. These results were corroborated by Myers et al. with use of high intensity AT in the same group of patients [95]. Furthermore, some authors have demonstrated an increase of ventricular filling, and therefore, an improvement of $\dot{V}O_{2peak}$ with AT. These results were corroborated by Malfatto et al. that added other findings as an increase in LV compliance after AT [90]. Additionally, improvement in chronotropic

Table 3 Description of aerobic exercise included in systematic review and meta-analysis

Study [ref], year	Study, sample	Sample size (*n*)	Age (years) (mean + SD)	Outcomes	Intervention description	Frequency (days/week)	Session duration (min)	Program duration (week)	PEDro score
Belardinelli et al. [78] 1995	HF CF II-III	AT 12 CG 13	55 ± 7 54 ± 6	LVEF	60% $\dot{V}O_{2\ peak}$ (cycle)	3	40	8	6
Belardinelli et al. [79] 1996	HF LVEF < 30%	AT 22 CG 21	55 ± 7 54 ± 6	$\dot{V}O_2$ peak + LVEF	60% $\dot{V}O_{2\ peak}$ (cycle)	3	60	8	6
Kiilavuori et al. [80] 1996	HF FC II-III/LVEF < 30%	AT 12 CG 15	52 ± 7 52 ± 9	$\dot{V}O_2$ peak + LVEF	60–70% $\dot{V}O_{2\ peak}$ (cycle)	3	30	30	5
Willenheimer et al. [81] 1998	HF FC I-III/LVEF < 40%	AT 22 CG 27	64 ± 5 63 ± 3	$\dot{V}O_2$ peak	80% $\dot{V}O_{2\ max}$ (cycle)	3	45	16	5
Sturm et al. [82] 1999	HF FC II-III/LVEF < 25%	AT 13 CG 13	55 ± 9 53 ± 9	$\dot{V}O_2$ peak	50% $\dot{V}O_{2\ peak}$ (cycle + step)	3	50	12	6
Belardinelli et al. [9] 1999	HF FC II-IV/LVEF < 30%	AT 50 CG 49	56 ± 7 53 ± 9	$\dot{V}O_2$ peak + LVEF + LVEDV	60% $\dot{V}O_{2\ peak}$ (cycle)	Phase I: 3 Phase II: 2	60	Phase I: 8 Phase II: 48	7
Keteyian et al. [83] 1999	HF FC II-III/LVEF < 35%	AT 21 CG 22	55 ± 12 57 ± 12	$\dot{V}O_2$ peak	50–80% HRR (cycle + treadmill)	3	30	24	4
Wielenga et al. [84] 1999	HF FC II-III/LVEF < 30%	AT 35 CG 32	62.4 ± 1.5 64.6 ± 1.4	$\dot{V}O_2$ peak	Interval training / At least 20 min at THR (cycling, walking and ball-game)	3	30	NR	5
Hambrecht et al. [85] 2000	HF FC I-III/LVEF < 40%	AT 31 CG 33	54 ± 9 54 ± 8	$\dot{V}O_2$ peak + LVEF + LVEDV	70% $\dot{V}O_{2\ peak}$ (cycle)	7	Hosp: 4 × 10 Home: 20	Hosp: 2 Home: 24	6
Myers et al. [55] 2002	HF LVEF < 30%	AT 12 CG 12	52.8 ± 12 58.2 ± 6	$\dot{V}O_2$ peak + LVEF + LVEDV	60–80% $\dot{V}O_{2\ peak}$ + BORG (13–15)	5	45	8	5
Giannuzzi et al. [86] 2003	HF FC II-III/LVEF < 35%	AT 45 CG 45	60 ± 7 61 ± 7	$\dot{V}O_2$ peak + LVEF + LVEDV	60% $\dot{V}O_{2\ peak}$ (cycle)	3 to 5	Superv: 30 / Not superv: >30	24	5
Corvera-Tyndel et al. [87] 2004	HF FC II-IV/LVEF < 35%	AT 42 CG 37	63.8 ± 10.1 61.3 ± 11.1	$\dot{V}O_2$ peak	Walking (40–60% FCmax)	5	60	12	6
van den Berg-Emons et al. [88] 2004	HF FC II-III/LVEF < 40%	AT 18 CG 16	58.6 ± 12.1 58.6 ± 10.6	$\dot{V}O_2$ peak	60% HRR (cycle + walking + games)	2	60	12	4
Koukouvou et al. [89] 2004	HF FC II-III/LVEF < 40%	AT 16 CG 10	52.3 ± 9.2 52.8 ± 10.6	$\dot{V}O_2$ peak	Circuit training (cycle + walking + step) 50–70% $\dot{V}O_{2\ peak}$ + Borg 12–14	4	60	24	5
Klocek et al. [90] 2005	HF FC II-III/LVEF < 35%	AT1 14 AT2 14 CG 14	54 ± 7 57 ± 8 55 ± 9	$\dot{V}O_2$ peak + LVEF	AT1: Constant load at 60% HRmax (5 × 4 min to 1 min rest) / AT2: Progressive workload (25 W every 5 min in 2 first months and 10 W every 5 min after 2 and 4 months)	3	25	24	5
Passino et al. [91] 2006	HF FC I-III/LVEF < 45%	AT 44 CG 41	60 ± 2 61 ± 2	$\dot{V}O_2$ peak + LVEF + LVEDV	60% HR at $\dot{V}O_{2\ peak}$ (cycle)	3	30	36	6
Klecha et al. [92] 2007	HF FC II-III/LVEF < 35%	AT 25 CG 25 CG 29	59.6 ± 10.2 61.2 ± 9.5 69.9 ± 6.3	$\dot{V}O_2$ peak + LVEF + LVEDV	80% HR at $\dot{V}O_{2\ peak}$ (cycle)	3	60	24	7
Mueller et al. [93] 2007	HF FC I-III/LVEF < 40%	AT 25 CG 25	55 ± 10 55 ± 10	$\dot{V}O_2$ peak	60–80% HRmax / Borg 12–14 (cycle + walking)	5	30	4	4

Table 3 (continued)

Study [ref], year		Study, sample	Sample size (*n*)		Age (years) (mean + SD)	Outcomes	Intervention description	Frequency (days/week)	Session duration (min)	Program duration (week)	PEDro score
Feiereisen et al. [12]	2007	HF FC II-III/LVEF < 35%	AT	15	59.4 ± 6.5	$\dot{V}O_2$ peak + LVEF + LVEDV	AT: 60–75% $\dot{V}O_{2\ peak}$ (cycle + treadmill)	3	40	13	5
			CG	15	55.5 ± 7.5						
Gademan et al. [94]	2008	HF FC II-III/LVEF < 40%	AT	20	60 ± 9	$\dot{V}O_2$ peak	50% peak Work SRT (Cycle)	3	75	10	6
			CG	14	63 ± 10						
Malfatto et al. [95]	2009	HF FC II-III/LVEF < 40%	AT	27	65 ± 11	$\dot{V}O_2$ peak + LVEF + LVEDV	60% $\dot{V}O_{2\ peak}$ (cycle or treadmill)	3	60	12	4
			CG	27	67 ± 9						
Mandic et al. [8]	2009	HF FC I-III/LVEF < 40%	AT	8	63 ± 11	$\dot{V}O_2$ peak + LVEF	AT: 50–70% HRR and BORG 11–14 (Cycle-15 min and Treadmill-15 min)	3	30	12	7
			CG	13	62 ± 13						
Van Craenenbroeck et al. [96]	2010	HF FC I-II/LVEF < 35%	AT	21	61.3 ± 2.2	LVEF	60% HR at RPC	3	60	24	5
			CG	17	63.4 ± 3						
O'Connor et al. [97]	2009	HF FC II-IV/LVEF < 30%	AT	1159	59.3 ± 9	$\dot{V}O_2$ peak	60–70% HRR (Walking, treadmill or Cycle)	3	35	12	7
			CG	1172	59.2 ± 8						
Erbs et al. [98]	2010	HF FC IIIb/LVEF < 30%	AT	18	60 ± 11	$\dot{V}O_2$ peak + LVEF + LVEDV	Hosp: 50% $\dot{V}O_{2\ peak}$; Home: 60% $\dot{V}O_{2\ peak}$	Hosp: 3 Home: 12	Hosp: 20 Home: 30	Hosp: 3 Home: 12	6
			CG	19	62 ± 12						
Lenk et al. [99]	2012	HF FC III/LVEF < 30%	AT	12	61 ± 11	$\dot{V}O_2$ peak	Hosp: 50% $\dot{V}O_{2\ peak}$; Home: 60% $\dot{V}O_{2\ peak}$	Hosp: 3 Home: 12	Hosp: 20 Home: 30	12	5
			CG	12	60 ± 10.7						
Alves et al. [10]	2012	HF FC I-IV/LVE-F < 45%	AT	34	62 ± 9.9	LVEF	5 × 3min: 70–75% and 1 min: 45–55% HRmax interval training (treadmill or cycle)	3	35	24	6
			CG	33	62 ± 9.9						
Myers et al. [100]	2012	HF LVEF < 35%	AT	24	55 ± 9	$\dot{V}O_2$ peak	60–80% HRR (walking + cycle)	7	Walking: 60 Cycle: 45	8	6
			CG	26	57 ± 7						
Sandri et al. [101]	2012	HF FC II-III/LVEF < 30%	AT	15	50 ± 5	$\dot{V}O_2$ peak + LVEF	70% $\dot{V}O_{2\ peak}$ (cycle)	4	20	4	6
			CG	15	49 ± 5						
Guazzi et al. [102]	2012	HF FC II-III/LVEF < 45%	AT	18	67.8 ± 5.9	$\dot{V}O_2$ peak	60–80% HRR (cycle)	4	40	24	
			CG	8	67.8 ± 5.9						
Huang et al. [103]	2014	HF LVEF < 35%	AT	33	60 ± 3	$\dot{V}O_2$ peak	Phase I: Exercise at LT; Phase II: Intervals 3 min: 40–80% $\dot{V}O_2$ reserve (cycle)	3	50	Phase I: 4 Phase II: 8	5
			CG	33	56 ± 4						
Chrysohoou et al. [104]	2014	HF FC II-IV/LVEF < 50%	AT	33	63 ± 9	$\dot{V}O_2$ peak	80%–100% WRpeak with 30 s rest	3	45	12	5
			CG	39	56 ± 11						

Legends: HF, heart failure; FC, functional class; LVEF, left ventricular ejection fraction; LVEDV, end diastolic volume; AT, aerobic training; CG, control group; HRmax, heart rate maximum; HRR, heart rate reserve; RMT, respiratory muscle training; RPC, respiratory point compensation; VT, ventilatory threshold; THR, target heart rate; NR, not reported; HRR, heart rate reserve; RPC, respiratory point compensation; WR, work rate

capacity is also important in improving exercise capacity - and $\dot{V}O_{2\ peak}$, with improvement of all HR components after the AT programs [56].

The peripheral effects of the RT method have also been described. Dieberg et al. [111] demonstrated that RT program with moderate intensity was able to generate reduction on autonomic activity, reducing peripheral vascular resistance (PVR) in HFrEF patients [111, 112]. Hambrecht et al. also described a reduction of sympathetic activity and an increase of vagal tone due to training resulting in a cardiovascular autonomic activity attenuation. Likewise, PVR reduction was related to arterial thickness reduction in patients with HFrEF [41]. Lastly, PVR reduction was related to central adaptations since a reducing of the LV afterload and an increasing of the LVEF and the cardiac output after an exercise program was described [12].

The improvement of $\dot{V}O_2$ peak after RT programs is also related to an increase of the muscular oxidative capacity through the increase of the citrate synthase and muscle ATP production [66, 115]. Similarly, Belardinelli et al. associate the $\dot{V}O_2$ peak increase after a low intensity AT program to an increase in mitochondrial density and muscle oxidative capacity [92].

However, it is extremely important to understand that the positive effects caused by RT should not be interpreted in this study as superior to the effects of AT, since the two interventions have important clinical relevance in the treatment of patients with FH.

The present study reveals that RT alone resulted in neutral effects on LVEF and on LVEDV. However, although our results and those of others [12, 18, 33] demonstrate no deleterious effect on the central hemodynamics of HF patients, RT should be performed cautiously with frequent monitoring. Our results reveal that RT is a safe training modality for patients with HF since no deleterious effects have been reported in studies in which RT was performed. Furthermore, there appears to be an important role of RT on cardiac remodeling with peripheral modifications, such as increased capillarization and oxidative capacity [116], lowering peripheral vascular resistance, and attenuating left ventricular afterload [8, 19, 60, 70, 114]. We should also consider the use of antiremodeling drugs as a potential confounding variable in the analyzed studies. Even though these drugs were used in similar doses in both the control and RT groups, the effects of these drugs in the control group may have attenuated cardiac remodeling variables and therefore statistically underestimated the differences between the study groups [12, 18].

This systematic review provides important information not addressed in previous meta-analyses of patients with HF. First, this study adds evidence with more recent studies comparing RT to a control group in patients with systolic HF on $\dot{V}O_2$ peak, LVEF and LVEDV. Second, this is the first meta-analysis to demonstrate significant improvement in $\dot{V}O_2$ with RT alone, updating the results presented in previous meta-analysis with fewer studies in which RT [13, 15].

Effects of combined exercise

Combined RT and AE and AE alone achieved a similar absolute effect regarding $\dot{V}O_2$ peak and LVEF. Only one study demonstrated analogous effect for these two interventions regarding LVEDV [45]. In our study, this exercise modality did not demonstrate additional effects on LVEF and LVEDV in comparison to the control group or resistance exercise alone. A previous meta-analysis by Haykowsky et al. [15] found that the positive effects of AE on these variables cannot be sustained with the addition of RT, suggesting that excessive pressure overload and stress on the ventricular wall from RT would worsen ventricular performance. However, several recent studies have demonstrated a change in this paradigm. Currently it is believed that the addition of RT to AE does not negatively effect cardiovascular function in patients with systolic HF, in any of the cardiac remodeling variables, such as preload, afterload and ventricular ejection fraction. Additionally, improved endothelial response and vascular resistance to exercise was observed after RT which may contribute to the improvement of LV performance [8, 11, 12, 17, 27, 57–59, 61, 64].

This is the first meta-analysis to demonstrate the favorable effect of combined RT and AE on functional capacity based on $\dot{V}O_2$ peak in patients with systolic HF. A previous meta-analysis did not identify the effects of combined RT and AE which appear to increase $\dot{V}O_2$ peak by a mean of 2.48 ml kg^{-1} min^{-1} According to current survival strata of systolic HF patients by levels of $\dot{V}O_2$ peak (< 8 ml kg^{-1} min^{-1}, 8 to 10 ml kg^{-1} min^{-1} and > 10 ml kg^{-1} min^{-1}) [117], that magnitude of increase in $\dot{V}O_2$ peak in our study may help improve prognosis in patients with HF, especially HF patients on a cardiac transplantation waiting list ($\dot{V}O_2$ peak < 8 ml kg^{-1} min^{-1}). Thus, the inclusion of combined exercise in cardiac rehabilitation programs is directly related to improvements in cardiorespiratory capacity in HF patients with reduced ejection fraction. Remarkably, a comparison of RT with AE alone produced similar effects on $\dot{V}O_2$ peak.

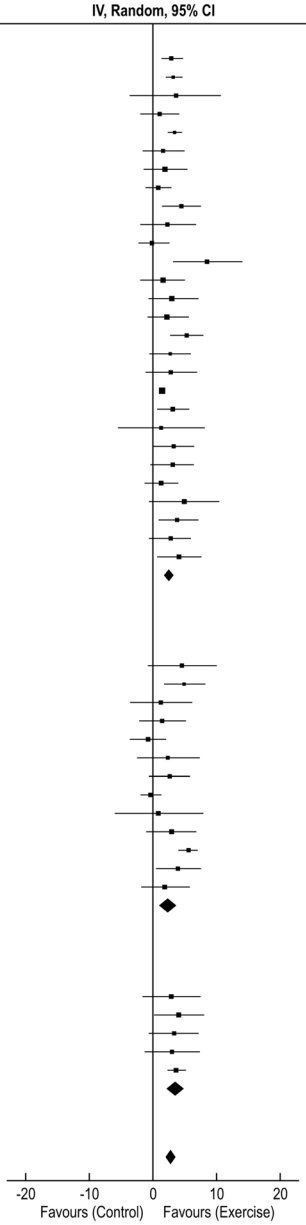
Including RT in rehabilitation programs for patients with HF has the potential to reverse or attenuate the peripheral vascular and skeletal muscle dysfunction secondary to HF. Furthermore, combined RT and AE has the additional potential to increase sub-maximal endurance compared to AE alone [11, 12].

The findings of the present meta-analysis on combined RT and AE are in agreement with previous studies, showing the effectiveness of combined exercise on either the improvement or the prevention of a worsening in $\dot{V}O_2$ peak in patients with HF which appears to be directly related to the adherence of patients to exercise training in rehabilitation programs [8].

A

Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Aerobic vs Control									
Belardinelli 1995	2.8	2.8	18	-0.1	1.34	9	3.9%	2.90 (1.34, 4.46)	1995
Belardinelli 1996	2.3	1.76	21	-0.9	2.26	22	4.4%	3.20 (1.99, 4.41)	1996
Killavouri 1996	2.4	10.28	12	-1	7.67	15	0.6%	3.40 (-3.59,10.39)	1996
Willenheimer 1998	0.9	5.2	22	-0.1	5.3	27	2.3%	1.00 (-1.95, 3.95)	1998
Belardinelli 1999	4.2	2.23	50	0.8	2.82	49	4.7%	3.40 (2.40, 4.40)	1999
Kateyian 1999	2.3	5.21	21	0.7	5.6	22	2.0%	1.60 (-1.63, 4.83)	1999
Sturm 1999	2.6	4.46	13	0.7	4.3	13	1.9%	1.90 (-1.47, 5.27)	1999
Wielenga 1999	1.4	4.17	35	0.6	4.79	32	3.1%	0.80 (-1.36, 2.96)	1999
Hambrecht 2000	4.8	6.1	31	0.3	6.08	33	2.3%	4.50 (1.51, 7.49)	2000
Myers 2002	3.6	6.44	12	1.3	3.81	12	1.4%	2.30 (-1.93, 6.53)	2002
Corvera-Tindel 2004	1	5.3	42	1	5.3	37	2.9%	0.00 (-2.34, 2.34)	2004
Koukouvou 2004	8	6.5	16	-0.6	7.1	10	1.0%	8.60 (3.17, 14.03)	2004
Vandeberg 2004	1.2	5.8	18	-0.3	4.7	16	1.8%	1.50 (-2.03, 5.03)	2004
Passino 2006	2	9.37	44	-1	9.04	41	1.6%	3.00 (0.91, 6.91)	2006
Feiereisen 2007	1.6	4.15	15	-0.6	5.16	15	2.0%	2.20 (-1.15, 5.55)	2007
Klecha 2007	4.6	4.78	25	-0.7	4.06	25	2.8%	5.30 (2.84, 7.76)	2007
Mueller 2007	3.9	6.3	25	1.3	5	25	2.1%	2.60 (-0.55, 5.75)	2007
Gademan 2008	2.5	6.5	20	-0.2	5.2	14	1.6%	2.70 (-1.24, 6.64)	2008
O´Connor 2009	1.54	0.22	1159	0.18	0.28	1172	5.5%	1.36 (1.34, 1.38)	2009
Malfatto 2009	3	4.52	27	-0.2	5.5	27	2.5%	3.20 (0.51, 5.89)	2009
Mandic 2009	1.3	8.8	12	0.1	8.55	13	0.7%	1.20 (-5.61, 8.01)	2009
Erbs 2010	2.5	4.59	18	-0.7	5.3	19	2.1%	3.20 (0.01, 6.39)	2010
Lenk 2011	2.64	3.94	12	-0.48	4.24	12	2.0%	3.12 (-0.15, 6.39)	2011
Guazzi 2012	1.5	5.67	20	0.3	2.14	18	2.6%	1.20 (-1.47, 3.87)	2012
Sandri 2012	4.8	8.48	15	-0.2	6.79	15	0.9%	5.00 (-0.50, 10.50)	2012
Myers 2012	4.67	6.16	24	0.73	5.06	26	2.1%	3.94 (0.80, 7.08)	2012
Huang 2014	2.2	6.2	33	-0.5	7.31	33	2.0%	2.70 (-0.57, 5.97)	2014
Chryssohoou 2014	5	7.81	33	1	7.21	39	1.9%	4.00 (0.50, 7.50)	2014
Subtotal (95% CI)			**1793**			**1791**	**64.7%**	**2.63 (1.96, 3.29)**	
Heterogeneity: Tau² = 1.13; Chi² = 64.95, df = 27 (P < 0.0001); I² = 58%									
Test for overall effect: Z = 7.76 (P < 0.00001)									
Combined vs Control									
Stolen 2003	5.2	6.62	9	0.6	5.1	11	1.0%	4.60 (-0.67, 9.87)	2003
Roveda 2003	5.8	3.6	7	0.9	2.82	9	2.0%	4.90 (1.66, 8.14)	2003
Sabelis 2004	0.3	7	16	-1	6.72	13	1.1%	1.30 (-3.71, 6.31)	2004
Senden 2005	0.7	7.3	25	-0.7	6.3	36	1.8%	1.40 (-2.12, 4.92)	2005
Josdolttir 2006	-0.16	4.57	21	0.55	5.1	22	2.3%	-0.71 (-3.60, 2.18)	2006
De Mello Franco 2006	2.2	7.6	17	-0.2	6.15	12	1.1%	2.40 (-2.62, 7.42)	2006
Feiereisen 2007	2	3.32	15	-0.6	5.16	15	2.2%	2.60 (-0.51, 5.71)	2007
Dracup 2007	0.3	5.3	86	0.6	5.5	87	3.9%	-0,30 (-1.91, 1.31)	2007
Mandic 2009	1	9.14	12	0.1	8.55	13	0.6%	0.90 (-6.05, 7.85)	2009
Antunes-Correa 2014	3	5.82	17	0	5.82	17	1.6%	3.00 (-0.91, 6.91)	2014
Meirelles 2014	5.8	2.25	15	0.1	1.8	15	4.1%	5.70 (4.24, 7.16)	2014
Chrysohoou 2014	5	7.21	33	1	7.81	39	1.9%	4.00 (0.53, 7.47)	2014
Groehs 2015	3	5.09	13	1	5.09	13	1.6%	2.00 (-1.94, 5.91)	2015
Subtotal (95% CI)			**286**			**302**	**25.2%**	**2.48 (0.88, 4.09)**	
Heterogeneity: Tau² = 5.26; Chi² = 39.00, df = 12 (P = 0.0001); I² = 69%									
Test for overall effect: Z = 3.03 (P = 0.002)									
Resistance vs Control									
Tyni-Lenné 2001	1.1	6	16	-1.6	4.8	8	1.3%	2.70 (-1.74, 7.14)	2001
Selig 2004	1.8	5.4	14	-2.1	6	19	1.6%	3.90 (-0.01, 7.81)	2004
Feiereisen 2007	2.6	5.42	15	-0.6	5.16	15	1.7%	3.20 (-0.59, 6.99)	2007
Willians 2007	1.7	3.3	7	-1.3	4.6	6	1.3%	3.00 (-1.42, 7.42)	2007
Maiorana 2011	2.7	1.62	12	-1	1.7	12	4.3%	3.70 (2.37, 5.03)	2011
Subtotal (95% CI)			**64**			**60**	**10.2%**	**3.57 (2.45, 4.68)**	
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 4 (P = 0.99); I² = 0%									
Test for overall effect: Z = 6.26 (P < 0.00001)									
Total (95% CI)			**2143**			**2153**	**100.0%**	**2.70 (2.11, 3.28)**	

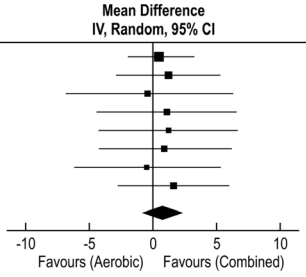
Heterogeneity: Tau² = 1.64; Chi² = 130.08, df = 45 (P < 0.00001); I² = 65%
Test for overall effect: Z = 9.03 (P < 0.00001)
Test for subgroup differences: Chi² = 2.20, df = 2 (P = 0.33); I² = 9.3%



B

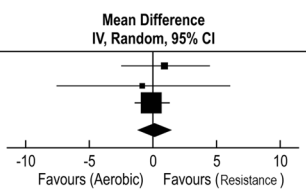
Study or Subgroup	Combined Mean	SD	Total	Aerobic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Feiereisen 2007	2	3.32	15	1.6	4.15	15	33.7%	0.40 (-2.29, 3.09)	2007
Beckers 2008	2.1	6.87	28	1	8.76	30	14.9%	1.10 (-2.94, 5.14)	2008
Mandic 2009	1.7	7.5	12	2.1	9.06	12	5.5%	-0.40 (-7.05, 6.25)	2009
Bouchla 2010	2.3	6.78	10	1.3	5.6	10	8.2%	1.00 (-4.45, 6.45)	2010
Anagnostakou 2011	2.6	8.7	14	1.5	5.44	14	8.4%	1.10 (-4.27, 6.47)	2011
Laoutaris 2013	2.8	8.09	13	1.9	5.45	14	8.9%	0.90 (-4.34, 6.14)	2013
Keast 2013	1.7	9.88	27	2.2	11.46	27	7.5%	-0.50 (-6.21, 5.21)	2013
Georgantas 2014	2.8	8	22	1.3	6.3	20	13.0%	1.50 (-2.84, 5.84)	2014
Total (95% CI)			**141**			**142**	**100.0%**	**0.69 (-0.87, 2.25)**	

Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 7 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)



Study or Subgroup	Resistance Mean	SD	Total	Aerobic Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Feiereisen 2007	2.6	5.42	15	1.6	4.15	15	15.0%	1.00 (-2.45, 4.45)	2007
Jakovljevic 2010	1	6.4	10	1.8	9.33	11	3.9%	-0.80 (-7.59, 5.99)	2010
Maiorana 2011	2.7	1.62	12	2.7	2.06	12	81.2%	0.00 (-1.48, 1.48)	2011
Total (95% CI)			**37**			**38**	**100.0%**	**0.12 (-1.22, 1.45)**	

Heterogeneity: Chi² = 0.34, df = 2 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.86)



◀ **Fig. 2** **a** Comparison of $\dot{V}O_2$ peak between aerobic, combined, and resistance exercise compared to control participants. **b** Comparison with combined versus aerobic and resistance versus aerobic exercise. $\dot{V}O_2$, peak oxygen consumption

Strengths and limitations

A modest to high heterogeneity was identified in the meta-analyses, especially in the AE studies due mostly to the inclusion of HF-Action study (I^2 = 58%). To address this,

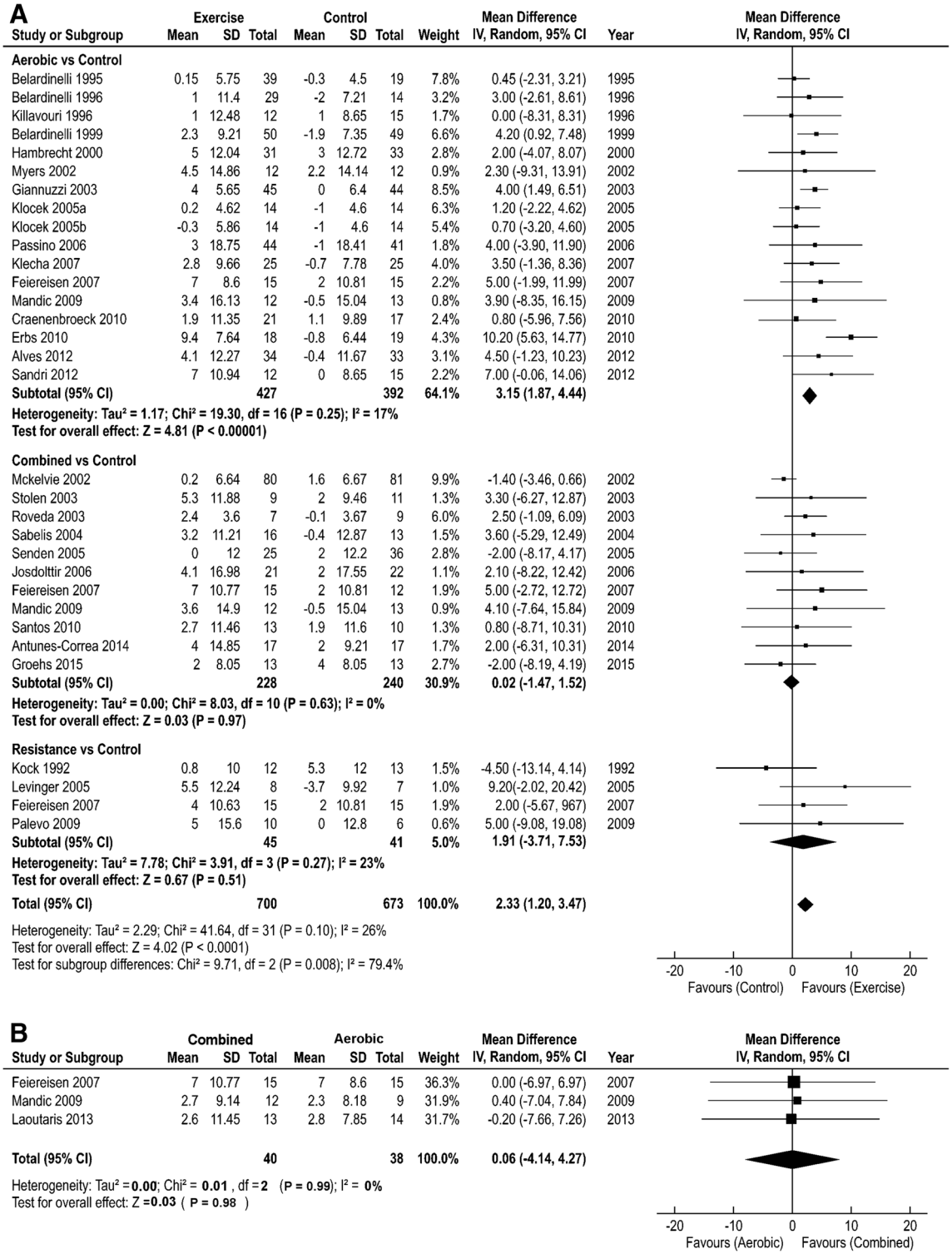


Fig. 3 **a** Comparison of LVEF between aerobic, combined and resistance exercise compared to control participants. **b** Comparison with combined versus aerobic exercise. LVEF, left ventricular ejection fraction

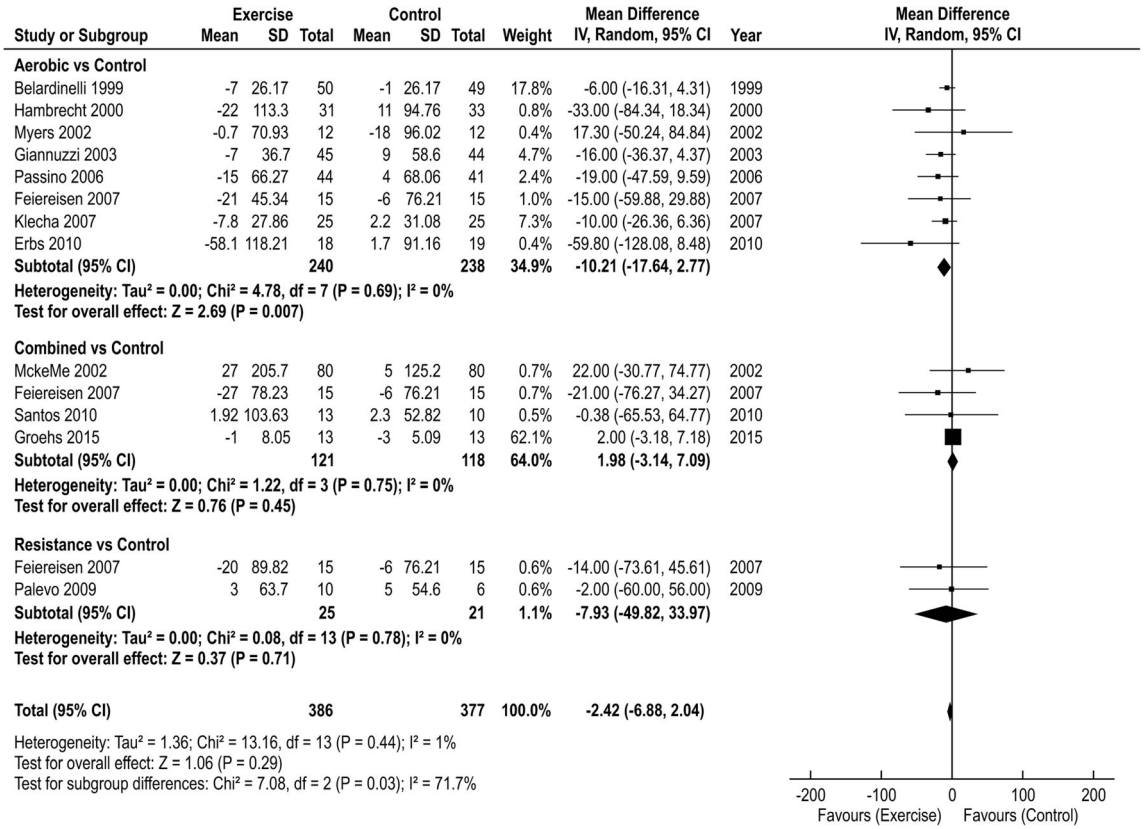


Fig. 4 Comparison of LVEDV between aerobic, combined and resistance exercise *compared to* control participants. LVEDV, left ventricular end diastolic volume

we have performed subgroup analyses. Also, we excluded clinical trials (n = 2) with older patients which resulted in a less heterogeneity among the included studies (I^2 < 50%) in analyses. The general quality of the included studies was low (mean score = 5.62, from 0 to 10), reflecting the possibility of increased risk of bias in some studies. The quality of the included studies in this meta-analysis was performed using PEDro scale which has been tested and confirmed in previous studies, demonstrating its ability to evaluate the quality of clinical trials [118, 119]. The quality of the included studies may have contributed to the level of heterogeneity observed in some of our analyses.

Conclusions

The most compelling finding from our study is that RT, either alone or combined with AE is an effective treatment modality for HF patients with reduced ejection fraction with a positive impact on $\dot{V}O_2$ peak. This study shows that RT is an effective option to minimize the effects on cardiac remodeling mechanism, as well as an excellent risk-benefit ratio since no adverse events were observed in any study in which RT was performed that was included in this meta-analysis.

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Compliance with ethical standards

Conflict of interest Author Francisco V. Santos declares that he has no conflict of interest.

Author Gaspar R. Chiappa declares that he has no conflict of interest.

Author Sergio Henrique Rodolpho Ramalho declares that he has no conflict of interest.

Author Alexandra Correa Gervazoni Balbuena de Lima declares that she has no conflict of interest.

Author Fausto Stauffer Junqueira de Souza declares that he has no conflict of interest.

Author Lawrence P. Cahalin declares that he has no conflict of interest.

Author João Luiz Quagliotti Durigan declares that he has no conflict of interest.

Author Isac de Castro declares that he has no conflict of interest.

Author Gerson Cipriano Jr. declares that he has no conflict of interest.

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

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