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The effect of resistance training on clinical outcomes in heart failure: A systematic review and meta-analysis☆

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ABSTRACT

Objectives: To quantify the change in effect sizes, for selected clinical outcome measures, in people with heart failure, from resistance exercise, either in isolation, or in combination with aerobic training.
Background: Most exercise training data in heart failure, relates to aerobic exercise, we sought to provide current evidence for the benefits of resistance training in this population.
Methods: We conducted a MEDLINE search (1985 to May 1, 2016), for exercise based rehabilitation trials in heart failure, using search terms 'resistance training, combined training, left ventricular dysfunction, peak VO_2, cardiomyopathy and systolic heart dysfunction'.
Results: The 27 included studies provided a total of 2321 participants, 1172 in an intervention and 1149 in either sedentary controls or aerobic exercise only groups, producing over 31,263 patient-hours of training. Mortality, hospitalization, resting blood pressure and Left ventricular fraction were all unchanged with resistance or combined aerobic and resistance training. Peak VO_2 was improved in combined exercise vs. control MD of 1.43 $ml \cdot kg^{-1} \cdot min^{-1}$ (95% CI 0.63, 2.23, $p = 0.0004$; and in resistance vs. control MD 3.99 $ml \cdot kg^{-1} \cdot min^{-1}$ (95% CI 1.47, 6.51, $p = 0.002$). Quality of Life (MLwHFQ) was improved in combined vs. control MD −8.31 (95% CI −14.3, −2.33, $p = 0.006$). Six-minute walk distance was improved combined exercise vs. control, MD 13.49 m (95% CI 1.13, 25.84, $p = 0.03$); and resistance vs. control MD 41.77 m (95% CI 21.90, 61.64, $p < 0.0001$): SMD 1.25 (95%CI 0.53, 1.98, $p = 0.0007$).
Conclusions: Resistance only or combined training improves peak VO_2, quality of life and walking performance in heart failure patients.

1. Introduction

Meta-analyses have shown limited evidence that resistance exercise training is beneficial in heart failure patients [1,2]. As heart failure patients are severely de-conditioned, aerobic, resistance or a combination of these types of exercise is likely to be beneficial, however the effects of aerobic exercise on physical measures of clinical status have been the focus of the majority of studies to date and the benefits of resistance exercise alone, or in combination with aerobic exercise, are less clear. Aerobic exercise has been shown, in heart failure patients, to improve peak VO_2 [3], left ventricular ejection fraction [1], endothelial function [4] and serum levels of natriuretic peptides [5] and pro-inflammatory cytokines [6,7]. Quality of life [8] is also improved with exercise training and may be associated with improved morbidity and survival [9].

Exercise training is considered the cornerstone of non-pharmacological heart failure therapy, with aerobic exercise most often the mainstay of this type of therapy. Moderate intensity aerobic exercise is well tolerated by most people with heart failure and is not suspected to detract from exercise adherence. That said, higher intensity exercise may be superior for eliciting health benefits in heart failure patients [10,11] and resistance exercise is usually performed at vigorous intensity or higher and may therefore offer desirable benefits. The number of available resistance training studies is considerably fewer than the number of published aerobic exercise training studies.

Previously meta-analyses were only able to pool data resulting in forest plots from only one to four studies [1,2]. Since the last search attempt for the purpose of data pooling almost seven years have passed and the publication of nine new resistance training trials may have yielded additional new information [12–20] not included in the most recent meta-analysis of only 8 included trials and 241 participants [2].

We conducted a preliminary, unpublished, systematic analysis of all clinical randomized, controlled, resistance-only, or combined resistance and aerobic exercise training trials in heart failure with reduced ejection fraction (HFrEF) patients. We aimed to determine via systematic review

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and meta-analysis to quantify any resistance exercise induced changes in selected clinical markers, in heart failure patients. Secondly, we wished to establish if effect sizes were comparable varied with the size of change previously observed from aerobic exercise training.

2. Methods

2.1. Search strategy

Studies were identified through a MEDLINE search strategy and a Cochrane database search. The search strategy was broad as to catch all available studies. Our MEDLINE search criteria included both MeSH and free text terms including Heart Failure, Left Ventricular Failure and Resistance training and Weight Training, see PubMed search strategy in Supplementary Files. These searches were limited to prospective randomized or controlled trials and human studies; and no restrictions on the year of publication. The search was restricted to English language papers. Reference list of papers and latest editions of relevant journals which were not available online were scrutinized for new references. Full articles were read and assessed by two reviewers (CO and DJ) for relevance and study eligibility. Disagreement on methodology were resolved by discussion and a third reviewer (NS) adjudicated over any disputes. One study author was contacted and requested to provide further data but did not do so.

2.2. Study selection

Included studies were randomized controlled design of resistance exercise training in chronic heart failure patients with reduced ejection fraction (HFrEF). Studies of heart failure patients with preserved ejection fraction (HFpEF) were excluded as we wished to avoid the notion that we were comparing 'apples and oranges' and the HFpEF patients would have made up a disproportionate (fewer) number of the total patients with only one study identified during selection (Edelmann et al., 2011). All published studies included in this systematic review are comparison studies between groups with a resistance exercise intervention vs. control, a combined aerobic and resistance exercise intervention vs. control or a combined aerobic and resistance exercise intervention vs. aerobic exercise alone. Reviewers categorized the studies into the three above categories for analysis based upon the methods section of each paper detailing the intervention.

Records were initially identified through database searching and additional records from the reference list were added. Only the principal study with the greatest subjects was included where multiple publications existed from the same dataset. After initial screening of titles, irrelevant studies were removed, which include over-lapping studies, abstracts and irrelevant articles such as editorials and discussion papers that did not match the inclusion criteria. Duplicate papers were then identified and removed. We excluded a further studies due to study design (Not RCT's); insufficient and/or irrelevant data for analyses, patient populations having HFpEF and non-exercise interventions.

2.3. Outcome measures

We recorded the following data; mortality, hospitalizations, change in peak VO_2 (baseline vs. post-intervention), change in quality of life, change in Left Ventricular Ejection Fraction (LVEF%), change in resting systolic blood pressure, change in 6-min walk test and change in heart rate; resting and peak.

2.4. Data synthesis

Revman 5.3 (Nordic Cochrane Centre, Denmark) was used to complete the meta-analysis and generate forest plots. Pooled data are presented as mean differences. We chose a random effects model as we anticipated some heterogeneity. A minimum of three studies was required for forest plots. Some studies used more than one intervention group, but the same people were only represented once in our forest plots.

Meta-analyses were completed for continuous data by using the change in the mean and standard deviation of outcome measures. It is an accepted practice to only use post-intervention data for meta-analysis but this method assumes that random allocation of participants always creates intervention groups matched at baseline for age, disease severity etc. Change in post-intervention mean was calculated by subtracting baseline from post-intervention values. Data required was either (i) 95% confidence interval data for pre–post-intervention change for each group or when this was unavailable, (ii) actual p values for pre–post-intervention change for each group or if only the level of statistical significance was available, or (iii) we used default p values e.g. $p < 0.05$ becomes $p = 0.049$, $p < 0.01$ becomes $p = 0.0099$ and p = not significant becomes $p = 0.05$. For dichotomous data odds ratio were reported, for continuous data mean differences (MD) and forest plots were provided. We also provided standardized mean differences (SMD) to give readers an idea of effect size. We used a 5% level of significance and 95% confidence intervals.

2.5. Statistical analyses

Table 1 lists the meta-analyses conducted.

Table 1
Summary of analyses conducted.

Outcome	Combined vs. control	Resistance vs. control	Combined vs. aerobic
Mortality	X		
Hospitalization	X		
Peak VO_2	X	X	X
Quality of life	X		
LVEF	X	X	
Resting blood pressure	X		
6 minute walk distance	X	X	
Resting heart rate	X		
Peak heart rate	X	X	

2.6. Heterogeneity

Heterogeneity was quantified using the I^2 test [21], as it does not inherently depend upon the number of studies considered. The I^2 statistics were presented, to gauge the degree of heterogeneity present in sample [21,22]. I^2 values range from 0% (homogeneity) to 100% (greater heterogeneity).

2.6.1. Publication bias

Egger plots [23] were provided to assess the risk of publication bias (see Supplementary Files).

2.6.2. Risk of bias assessment

We assessed study quality with regard to: eligibility criteria specified, random allocation of participants, allocation concealed, similarity groups at baseline, assessors blinded, outcome measures assessed in 85% of participants and intention to treat analysis. Study quality was assessed by using the TESTEX scale [24] — the Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX) — a study quality and reporting

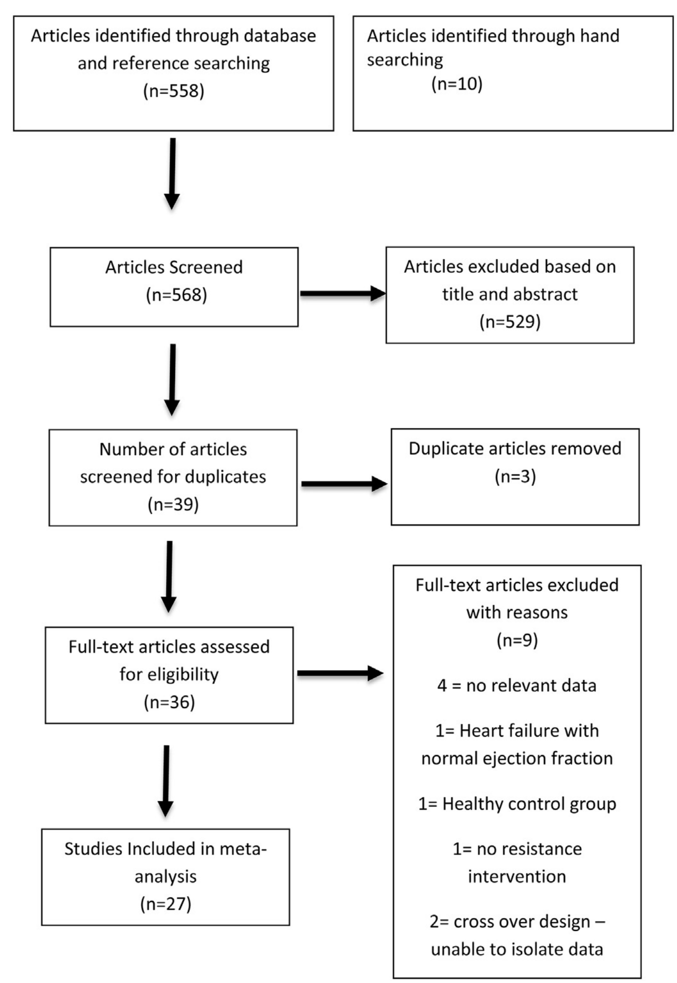

Fig. 1. PRISMA statement.

Table 2
Included studies.

Studies of combined aerobic and resistance training vs. control (n = 18)						
Outcome measure	Studies analyzed	Number in CAR	Number in control	Effect (95% CI)	p value	i^2
Mortality	9	786	800	OR 0.97 (0.63, 1.50)	NS 0.9	0%
Hospitalizations	8	395	394	OR 0.66 (0.48, 0.91)	p = 0.01	29%
Peak VO_2	12	218	195	MD 0.48 (0.17, 0.79)	p = 0.002	88%
QoL	8	373	375	MD −5.27 (−8.22, −2.33)	p = 0.0005	72%
LVEF%	5	145	135	MD −0.34 (−0.60, −0.07)	p = 0.01	68%
SBP-resting	3	113	107	MD −2.03 (−3.67, −0.39)	p = 0.02	84%
6-Min walk	7	324	341	MD −2.11 (−4.61, 0.40)	NS 0.1	82%
rHR	3	48	37	MD −5.13 (−8.37,-1.88)	p = 0.002	57%
pHR	4	59	45	MD −1.02 (−1.87, −0.17)	p = 0.02	79%

Studies of resistance training vs. control n = 7						
Outcome Measure	Studies analyzed	Number in RG	Number in control	Effect (95% CI)	p value	i^2
Peak VO_2	4	78	64	MD 4.10 (3.35, 4.85)	p < 0.00001	91%
LVEF%	4	71	53	MD −0.57 (−1.97, 0.84)	NS 0.43	79%
6-Min walk	2	26	14	MD 40.67 (24.50, 56.83)	p < 0.00001	29%
pHR	3	56	41	MD 4.56 (2.50, 6.61)	p = 0.0003	81%

Studies of combined aerobic and resistance vs. aerobic training						
Outcome Measure	Studies analyzed	Number in CAR	Number in aerobic	Effect (95% CI)	p value	i^2
Peak VO_2	6	105	105	MD 0.61 (−0.14, 1.36)	p = 0.11	0%

assessment tool, designed specifically for use in exercise training studies. The main point of difference in TESTEX is that there are accommodations for: Activity monitoring in control groups to measure crossover to exercise by sedentary control patients; assessment of the existence and method of activity monitoring in both exercise intervention and sedentary controls; assessment of whether the relative exercise intensity remained constant and therefore potentially avoided de-training as participants initially adapt to new exercise programs; assessment of whether periodic evidence-based adjustment of exercise intensity is reported exercise volume and exercise expenditure Information on all exercise characteristics (intensity, duration, frequency and mode) is provided to calculate exercise volume and exercise energy expenditure.

This tool is a 15-point scale (5 points for study quality and 10 points for reporting) and addresses previously unmentioned quality assessment criteria specific to exercise training studies. Two reviewers CO and DJ conducted the risk of bias assessment, NS was consulted of discrepancies occurred.

3. Results

3.1. Included studies

Five hundred and fifty eight records were initially identified through database searching and from the reference lists, 10 additional records were found by hand searching. We screened 568 articles and excluded

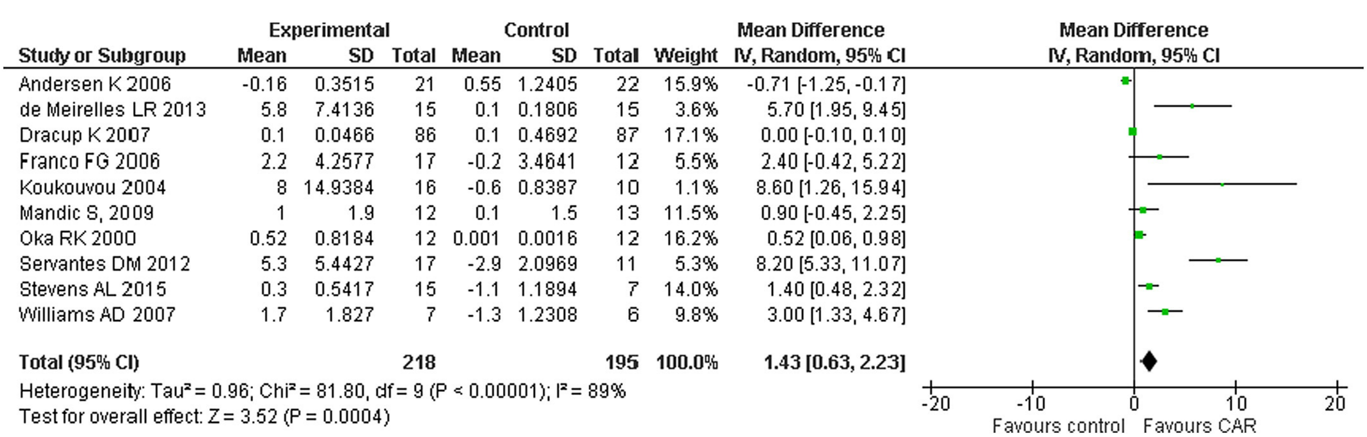

Fig. 2. Peak VO_2 combined versus control groups.

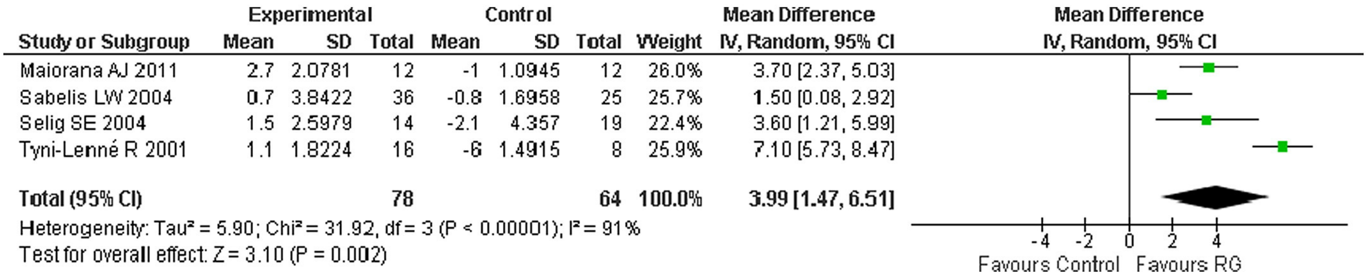

Fig. 3. Peak VO_2 resistance versus control groups.

529 based upon title and abstract. Three were duplicates, where only the principal study with the greatest subjects was included where multiple publications existed from the same dataset. The full text of 36 studies was assessed for eligibility and 9 of these were excluded. We excluded a further two studies as we were unable to separate data from the different phases of a crossover study design; five for insufficient and/or irrelevant data for analyses, one due to the patient population having HFpEF and one for including inspiratory muscle training. Twenty seven studies were included in the meta-analyses (see Consort Statement, Fig. 1). All excluded randomized, controlled trials of resistance exercise training in heart failure are listed in Supplementary Files.

Twenty seven studies were included, producing 29 intervention groups. In total there were 5 groups that compared a combined aerobic and resistance exercise vs. aerobic exercise, 6 groups compared resistance exercise vs. control, 18 groups compared a combined aerobic and resistance exercise with control. The 27 studies provided a total of 2321 participants, 1172 exercising and 1149 controls, totaling 31,263 patient-hours of exercise training.

3.2. Exercise training parameters

Exercise studies varied in duration from 6 to 26 weeks. Exercise intensity varied from 60–80% of 1 Repetition maximum. Frequency varied from 2–5 times weekly and session duration from 30 to 90 min. Details of the interventions in the included studies are detailed in Table 2.

4. Outcome measures

4.1. Mortality

Analysis of the nine combined aerobic and resistance exercise (CAR) vs. control groups ($I^2 = 0\%$) suggested combined training did not reduce mortality OR 1.00 (95% CI 0.64, 1.55, p = 0.99), Forest Plot in Supplementary Files.

4.2. Hospitalization

Analysis of hospitalization in the 8 groups comparing combined aerobic and resistance exercise (CAR) vs. control $I^2 = 29\%$) reported no reduction in hospitalization OR 0.66 (95% CI 0.43, 1.00, p = 0.05) Forest Plot in Supplementary Files.

4.3. Peak VO_2

4.3.1. Combined aerobic and resistance exercise (CAR) vs. control

Ten studies ($I^2 = 79\%$) were analyzed showing an improvement in Peak VO_2 in the combined groups MD of 1.43 $ml \cdot kg^{-1} \cdot min^{-1}$ (95% CI 0.63, 2.23, p = 0.0004) Fig. 2: SMD 0.73 (95% CI 0.22, 1.23, p = 0.005).

4.3.2. Resistance exercise (RG) vs. control

Four studies ($I^2 = 91\%$) were analyzed showing an improvement in Peak VO_2 in the resistance groups MD 3.99 $ml \cdot kg^{-1} \cdot min^{-1}$ (95% CI 1.47, 6.51, p = 0.002) Fig. 3; SMD 1.72 (95% CI 0.52, 2.93, p = 0.005).

4.3.3. Combined aerobic and resistance (CAR) vs. aerobic

Six studies ($I^2 = 0\%$) showed no difference in peak VO_2 between combined and aerobic exercise groups, MD 0.61 $ml \cdot kg^{-1} \cdot min^{-1}$ (95% CI −0.14, 1.36, p = 0.11) Forest Plot in Supplementary Files: SMD 0.24 (95% CI −0.03, 0.51, p = 0.08).

4.3.4. Quality of life

Analysis of the 8 groups comparing combined aerobic and resistance exercise (CAR) vs. control ($I^2 = 72\%$) showed MLwHFQ score was improved in the CAR group MD −8.31 (95% CI −14.3, −2.33, p = 0.006) Fig. 4: SMD −0.32 (95%CI −0.58, −0.06, p = 0.01).

4.4. LVEF%

4.4.1. Combined aerobic and resistance exercise (CAR) vs. control

Five studies ($I^2 = 68\%$) showed no difference between CAR and control groups MD −0.68% (95% CI −2.48, 1.12, p = 0.46) Forest Plot in Supplementary Files: SMD −0.32 (95%CI −0.91, 0.28, p = 0.30).

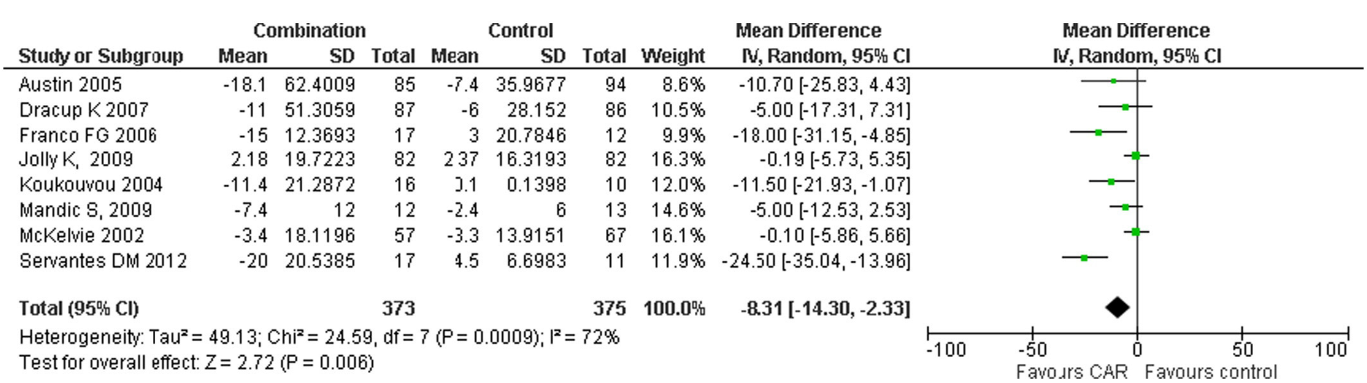

Fig. 4. Quality of life resistance versus control groups.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Andersen K 2006	37.1	44.1649	21	5.4	12.1793	22	17.3%	31.70 [12.14, 51.26]
Austin 2005	44.9	120.2384	85	-6.7	33.7665	94	12.7%	51.60 [25.14, 78.06]
Dracup K 2007	72.2	336.753	87	61.5	288.5577	86	1.7%	10.70 [-82.72, 104.12]
Gary RA 2012	46.4	46.9	12	-1.02	67.2	12	5.8%	47.42 [1.05, 93.79]
McKelvie 2002	17	8	64	20	9	75	30.1%	-3.00 [-5.83, -0.17]
Norman 2012	54.7	113.4891	19	32.3	69.015	20	3.8%	22.40 [-36.92, 81.72]
Witham 2005	1	2.9555	36	6	16.6418	32	28.6%	-5.00 [-10.85, 0.85]
Total (95% CI)			**324**			**341**	**100.0%**	**13.49 [1.13, 25.84]**

Heterogeneity: Tau² = 129.93; Chi² = 33.74, df = 6 (P < 0.00001); I² = 82%
Test for overall effect: Z = 2.14 (P = 0.03)

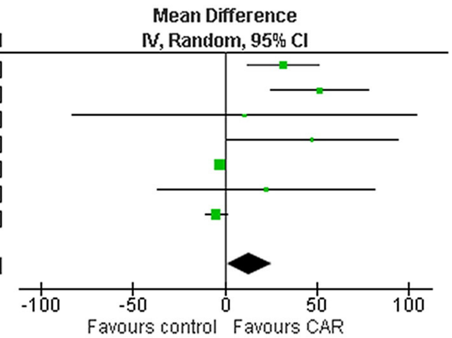

Fig. 5. Six minute walk distance combined versus control groups.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Palevo G 2009	17	23.6352	10	-17	16.1992	6	63.0%	34.00 [14.44, 53.56]
Tyni-Lenné R 2001	55	58.5434	16	0.0001	0.0001	8	37.0%	55.00 [26.31, 83.69]
Total (95% CI)			**26**			**14**	**100.0%**	**41.77 [21.90, 61.64]**

Heterogeneity: Tau² = 63.59; Chi² = 1.41, df = 1 (P = 0.24); I² = 29%
Test for overall effect: Z = 4.12 (P < 0.0001)

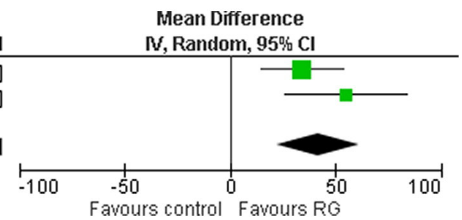

Fig. 6. Six minute walk distance resistance versus control groups.

4.4.2. Resistance exercise (RG) vs. control

Four studies ($I^2 = 79\%$) showed no difference between resistance and control groups MD 0.23% (95% CI −3.37, 3.82, p = 0.90) Forest Plot in Supplementary Files; SMD −0.06 (95%CI −0.84, 0.72, p = 0.88).

4.4.3. Resting systolic blood pressure

Analysis of the three studies comparing combined aerobic and resistance exercise (CAR) vs. control ($I^2 = 84\%$) found no significant difference in systolic blood pressure between groups MD −2.82 (95% CI −10.17, 4.53, p = 0.45) Forest Plot in Supplementary Files; SMD −0.49 (95% CI −1.44, 0.46, p = 0.31).

4.5. 6-Min walk test distance

4.5.1. Combined aerobic and resistance exercise (CAR) vs. control

Seven studies ($I^2 = 82\%$) showed a significant improvement in 6MWD in the CRA groups compared to control, MD 13.49 m (95% CI 1.13, 25.84, p = 0.03) Fig. 5; SMD 0.22 [95% CI −0.17, 0.60, p = 0.27].

4.5.2. Resistance exercise (RG) vs. control

Two studies ($I^2 = 29\%$) showed a significant improvement in the resistance groups compared to control, MD 41.77 m (95% CI 21.90, 61.64, p < 0.0001) Fig. 6: SMD 1.25 (95%CI 0.53, 1.98, p = 0.0007).

4.5.3. Resting heart rate

Analysis of the three groups comparing combined aerobic and resistance exercise (CAR) vs. control ($I^2 = 57$ showed a significant reduction in resting heart rate in the CAR groups MD −4.78 (95% CI −9.87, 0.31, p = 0.07) Forest Plot in Supplementary Files: SMD −0.55 (95% CI −1.25, 0.17, p = 0.13).

4.6. Peak heart rate

4.6.1. Combined aerobic and resistance exercise (CAR) vs. control

Analysis of four studies ($I^2 = 79\%$) showed no significant difference between groups, MD −0.56 (95% CI −6.07, 4.96, p = 0.84) Forest Plot in Supplementary Files: SMD −0.42 (95%CI −1.51, 0.67, p = 0.45).

4.6.2. Resistance exercise (RG) vs. control

Analysis of three studies ($I^2 = 59\%$) showed resistance exercise groups to have a higher peak heart rate compared to control MD 5.43 (95% CI 1.65, 9.21, p = 0.005) Fig. 7; SMD 0.85 (95% CI 0.42, 1.28, p < 0.0001).

4.6.2.1. Study quality. We examined several aspects of study quality of included studies. Median TESTEX score was 10 out of 15 (see Table 3). The distribution of scores was; 1 study scored 7, 3 scored 8, 5 scored 9, 6 scored 10, 6 scored 11, 5 scored 12 and 1 scored 13. Allocation concealment (only performed by 11 studies); Intention to treat analyses (only 5 studies); assessor blinding (only 5 studies); and activity monitoring (only 8 studies) in the comparator groups (sedentary or aerobic) were performed by less than 50% of included studies.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Koch 1992	3.7	6.1228	13	-0.4	0.5592	10	41.1%	4.10 [0.75, 7.45]
Sabelis LW 2004	2	5.911	36	-2	4.8452	25	46.3%	4.00 [1.29, 6.71]
Tyni-Lenné R 2001	3	3.2438	7	-12	11.4347	6	12.6%	15.00 [5.54, 24.46]
Total (95% CI)			**56**			**41**	**100.0%**	**5.43 [1.65, 9.21]**

Heterogeneity: Tau² = 6.12; Chi² = 4.92, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 2.82 (P = 0.005)

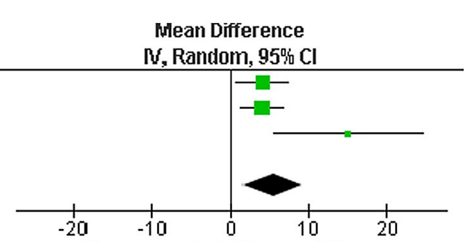

Fig. 7. Peak heart rate resistance versus control groups.

Table 3
Study quality (TESTEX) assessment.

Study name	Eligibility criteria specified	Randomly allocated participants	Allocation concealed	Groups similar at baseline	Assessors blinded	Outcome measures assessed >85% of participants[#]	Intention to treat analysis	Reporting of between group statistical comparisons	Point measures & measures of variability reported[*]	Activity monitoring in control group	Relative exercise intensity review	Exercise volume & energy expended	Overall TESTEX
Anagnostakou (2011)	Yes	Yes	Unclear	Yes	Unclear	No (1)	No	Yes (2)	Yes	No	Yes	Yes	9
Andersen (2006)	Yes	Yes	Yes	Yes	Unclear	Yes (2)	No	Yes (2)	Yes	No	Yes	Yes	11
Austin (2005)	Yes	Yes	Yes	Yes	Yes	Yes (2)	No	Yes (2)	Yes	No	No	No	10
Beckers (2008)	Yes	No	No	Yes	Unclear	Yes (2)	No	Yes (2)	Yes	Yes? (res vs. aerobic)	Yes	Yes	10
Bouchla (2011)	Yes	Yes	Unclear	Yes	Unclear	Yes (3)	No	Yes (2)	Yes	Yes (res vs. Aerobic)	Yes	Yes	12
DANREHAB (2008)	Yes	Yes	Yes	Yes	No	No (1)	Yes	Yes (2)	Yes	No	No	No	9
de Meirelles (2013)	Yes	Yes	Unclear	Yes	Unclear	Yes (1)	No	Yes (2)	No	No	No	Yes	7
Dracup (2007)	Yes	Yes	No	Yes	Yes	Yes (1)	Yes	Yes (2)	Yes	Yes	Yes	Yes	12
Gary (2012)	Yes	Yes	Yes	Yes	Unclear	No (2)	No	Yes (2)	Yes	No	Yes	Yes	11
Georgantas (2014)	Yes	Yes	Yes	Yes	Yes	No (2)	No	Yes (2)	Yes	Yes (res vs. aerobic?)	Yes	Yes	13
Franco (2006)	Yes	Yes	No	Yes	No	Yes (1)	Yes	Yes (2)	Yes	Yes	Yes	Yes	11
Jolly (2009)	Yes	Yes	No	Yes	No	Yes (2)	Yes	Yes (2)	Yes	No	Yes	No	10
Koch (1992)	No	Yes	Yes	Yes	Unclear	Yes (1)	No	Yes (2)	No	No	Yes	Yes	8
Koukouvou (2004)	Yes	Yes	Unclear	Yes	Unclear	Yes (3)	No	No	Yes	No	Yes	Yes	9
Majorana (2011)	Yes	Yes	Unclear	Yes	Unclear	Yes (2)	No	Yes (2)	Yes	No	Yes	Yes	10
Mandic (2009)	Yes	Yes	No	Yes	Yes	Yes (2)	Yes	Yes (2)	Yes	No	No	Yes	11
McKelvie (2002)	Yes	Yes	Yes	Yes	Unclear	Yes (3)	No	Yes (2)	Yes	No	Yes	Yes	12
Norman (2012)	Yes	Yes	Yes	Yes	Unclear	Yes (2)	No	No	Yes	No	No	Yes	8
Oka (2000)	Yes	Yes	Unclear	Yes	Unclear	Yes (3)	No	No	Yes	Yes	No	Yes	9
Pavelo (2009)	Yes	Yes	Unclear	Yes	Unclear	Yes (3)	No	No	Yes	No	Yes	Yes	9
Sabelis (2004)	Yes	Yes	Unclear	Yes	Unclear	No (2)	No	Yes (2)	Yes	No	Yes	Yes	10
Selig (2004)	Yes	Yes	Yes	Yes	Unclear	Yes (2)	No	Yes (2)	Yes	Yes	Yes	Yes	12
Servantes (2011)	Yes	Yes	Unclear	Yes	Unclear	Yes (2)	No	Yes (2)	Yes	Yes	Yes	Yes	11
Stevens (2015)	Yes	Yes	Unclear	Yes	Unclear	No (2)	No	Yes (2)	Yes	No	Yes	Yes	10
Tyni-Lenne (2001)	Yes	Yes	Unclear	Yes	Unclear	Yes (3)	No	Yes (2)	Yes	No	Yes	Yes	11
Williams (2007)	Yes	Yes	Yes	Yes	Unclear	No (1)	No	No	Yes	No	Yes	Yes	8
Witham (2005)	Yes	Yes	Yes	Yes	Yes	No (2)	No	Yes (2)	Yes	No	Yes	Yes	12
Totals	26	26	11	27	5	Median 2	5	Median 2	25	8	21	25	Median 10

[#] Three points possible: 1 point if adherence 85%, 1 point if adverse events are reported, and 1 point if exercise attendance is reported.
[*] Two points possible: 1 point if primary outcome is reported and 1 point if all other outcomes are reported.

4.7. Publication bias

Funnel (Egger) plots can be seen in the Supplementary Files, Figs. S10–S24. These analyses showed some evidence of publication bias.

5. Discussion

This meta-analysis of resistance training trials in heart failure patients has made current the relevant literature synthesis. Our work has, for the first time, also included analyses of combined aerobic and resistance training as well as resistance only interventions. Our work has increased the number of participants from about 240 to over 2300. Previously meta-analyses were only able to pool data resulting in forest plots from only one to four studies [1,2], our work has increased the statistical power of many outcomes. The 27 included studies in our work have provided data in 1172 exercising and 1149 controls, resulting in an aggregate of >31,000 patient-hours of exercise training. Since the last such attempt at data pooling, almost seven years ago, the 9 new trials have yielded additional new information. Our work shows that there are benefits elicited from resistance training to heart failure patients in terms of cardiorespiratory fitness (peak VO_2), quality of life (Minnesota living with heart failure questionnaire), global cardiac systolic function, resting blood pressure and heart rate and walking ability. Our work also reveals that resistance exercise is under utilized in heart failure patients.

Unsurprisingly there were an insufficient number of deaths to show a significant survival benefit. There was however evidence of a trend towards a reduction in incidence of hospitalization with combined aerobic and resistance training versus sedentary control. Again, we suspect an insufficient number of events means this analysis is underpowered with respect to mortality and hospitalization outcomes, until future resistance studies provide additional data. These data are similar to data from the current relevant Cochrane systematic review [25] that includes all randomized, trials of exercise training, but predominantly aerobic only interventions. Scrutiny of 95% CI's from our work and the Cochrane review, which do not overlap, suggest aerobic exercise alone may be superior to combined exercise training for reducing hospitalization.

As cardiorespiratory fitness is clearly linked to prognosis in heart failure [26] it is important to understand the relationship between exercise training modality and effect size for peak VO_2. Combined aerobic and resistance exercise showed only small improvement versus control and no significant improvement versus aerobic exercise, all that we can say for sure is that resistance exercise is superior to sedentary behavior in terms of improving peak VO_2. We should note that more than 4 $ml \cdot kg^{-1} \cdot min^{-1}$ improvement between resistance training versus control is a large effect size. This effect size is likely to elicit a number of favorable related outcomes including improved quality of life, lessening of symptoms and improved prognosis [26]. Aligned with this our analyses showed moderate improvement on six minute walk distance in resistance exercise versus control. The 2010 meta-analyses also found resistance training improved six minute walk distance [2].

Recent work has illustrated that quality of life in published exercise training studies in heart failure patients is most often measured by the Minnesota Living with Heart Failure Questionnaire [27]. That said, a number of other questionnaires have been employed, moreover about one third of existing data comes from the HF-ACTION study [28] that utilized the Kansas City Cardiomyopathy Questionnaire (KCCQ). Despite the difficulty in obtaining quality of life data post-exercise intervention we were able to report a large effect size for improvement in MLwHFQ score for comparisons of combined exercise versus sedentary control.

Absence of change in LVEF% in combined exercise versus control was not dissimilar to the work of Haykowsky [1]. The absence of change in LVEF in resistance exercise versus control contradicts, to some extent, Haykowsky's findings as he reported a large worsening of LVEF with resistance training by −4.5% [1]. Our contention is that resistance training may not be as detrimental to systolic function as once thought, after all Haykowsky's 2007 analysis [1] was based on a single study form 1992 [29], which was all the relevant data available at the time. Until now practitioners may have been tempted to use resistance exercise sparingly in heart failure patients and perhaps not at all in those with severe systolic dysfunction. The current analyses perhaps temper the current position and as such practitioners may be more willing to encourage their patients to take advantage of the benefits evident from resistance training.

Resting systolic blood pressure was decreased with combined exercise versus control. The 2 mm Hg reduction may not be clinically significant but may be less than expected from aerobic exercise training [30]. Resting heart rate showed a moderate reduction with combined exercise versus control but a change of -5 $beats \cdot min^{-1}$ may be equivalent to that expected from aerobic exercise [31]. Peak heart rate showed little change with combined versus control but a slight increase of 4–5 $beats \cdot min^{-1}$ in resistance exercise versus control. This increase in peak heart rate would facilitate a small increase in peak cardiac output and peak VO_2. The increase in cardiac output may result in improved contractile reserve which is associated with a more favorable prognosis in people with heart failure [32].

6. Conclusions

We were unable to find sufficient evidence for benefits in mortality, hospitalization, resting blood pressure and Left ventricular fraction, which were all unchanged with resistance or combined aerobic and resistance training. Resistance only or combined training improves peak VO_2, quality of life and walking performance in heart failure patients.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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References

[1] M.J. Haykowsky, Y. Liang, D. Pechter, L.W. Jones, F.A. McAlister, A.M. Clark, A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed, J. Am. Coll. Cardiol. 49 (24) (Jun 19 2007) 2329–2336.

[2] C.L. Hwang, C.L. Chien, Y.T. Wu, Resistance training increases 6-minute walk distance in people with chronic heart failure: a systematic review, J. Physiother. 56 (2) (2010) 87–96.

[3] N. Smart, T.H. Marwick, Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity, Am. J. Med. 116 (10) (May 15 2004) 693–706.

[4] R. Hambrecht, L. Hilbrich, S. Erbs, S. Gielen, E. Fiehn, N. Schoene, G. Schuler, Correction of endothelial dysfunction in chronic heart failure: additional effects of exercise training and oral L-arginine supplementation, J. Am. Coll. Cardiol. 35 (3) (Mar 1 2000) 706–713.

[5] N.A. Smart, M. Steele, Systematic review of the effect of aerobic and resistance exercise training on systemic brain natriuretic peptide (BNP) and N-terminal BNP expression in heart failure patients, Int. J. Cardiol. 140 (3) (Apr 30 2010) 260–265.

[6] N.A. Smart, M. Steele, The effect of physical training on systemic proinflammatory cytokine expression in heart failure patients: a systematic review, Congest. Heart Fail. 17 (3) (May-Jun 2011) 110–114.

[7] N.A. Smart, A.I. Larsen, J.P. Le Maitre, A.S. Ferraz, Effect of exercise training on interleukin-6, tumour necrosis factor alpha and functional capacity in heart failure, Cardiol. Res. Pract. 2011 (2011) 532620.

[8] B.A. Van Tol, R.J. Huijsmans, D.W. Kroon, M. Schothorst, G. Kwakkel, Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: a meta-analysis, Eur. J. Heart Fail. (May 16 2006).

[9] B. Fernhall, Long-term aerobic exercise maintains peak VO(2), improves quality of life, and reduces hospitalisations and mortality in patients with heart failure, J. Physiother. 59 (1) (Mar 2013) 56.

[10] H. Ismail, J.R. McFarlane, G. Dieberg, N.A. Smart, Exercise training program characteristics and magnitude of change in functional capacity of heart failure patients, Int. J. Cardiol. 171 (1) (Jan 15 2014) 62–65.

[11] H. Ismail, J.R. McFarlane, A.H. Nojoumian, G. Dieberg, N.A. Smart, Clinical outcomes and cardiovascular responses to different exercise training intensities in patients

with heart failure: a systematic review and meta-analysis, JACC. Heart Fail. 1 (6) (Dec 2013) 514–522.
[12] V. Anagnostakou, K. Chatzimichail, S. Dimopoulos, E. Karatzanos, O. Papazachou, A. Tasoulis, M. Anastasiou-Nana, C. Roussos, S. Nanas, Effects of interval cycle training with or without strength training on vascular reactivity in heart failure patients, J. Card. Fail. 17 (7) (Jul 2011) 585–591.
[13] A. Bouchla, E. Karatzanos, S. Dimopoulos, A. Tasoulis, V. Agapitou, N. Diakos, E. Tseliou, J. Terrovitis, S. Nanas, The addition of strength training to aerobic interval training: effects on muscle strength and body composition in CHF patients, J. Cardiopulm. Rehabil. Prev. 31 (1) (Jan-Feb 2011) 47–51.
[14] L.R. de Meirelles, C. Matsuura, C. Resende Ade, A.A. Salgado, N.R. Pereira, P.G. Coscarelli, A.C. Mendes-Ribeiro, T.M. Brunini, Chronic exercise leads to antiaggregant, antioxidant and anti-inflammatory effects in heart failure patients, Eur. J. Prev. Cardiol. 21 (10) (Oct 2014) 1225–1232.
[15] R.A. Gary, M.E. Cress, M.K. Higgins, A.L. Smith, S.B. Dunbar, A combined aerobic and resistance exercise program improves physical functional performance in patients with heart failure: a pilot study, J. Cardiovasc. Nurs. 27 (5) (Sep-Oct 2012) 418–430.
[16] A. Georgantas, S. Dimopoulos, A. Tasoulis, E. Karatzanos, C. Pantsios, V. Agapitou, A. Ntalianis, P. Roditis, J. Terrovitis, S. Nanas, Beneficial effects of combined exercise training on early recovery cardiopulmonary exercise testing indices in patients with chronic heart failure, J. Cardiopulm. Rehabil. Prev. 34 (6) (Nov-Dec 2014) 378–385.
[17] A.J. Maiorana, L.H. Naylor, A. Exterkate, A. Swart, D.H. Thijssen, K. Lam, G. O'Driscoll, D.J. Green, The impact of exercise training on conduit artery wall thickness and remodeling in chronic heart failure patients, Hypertension 57 (1) (Jan 2011) 56–62.
[18] J.F. Norman, B.J. Pozehl, K.A. Duncan, M.A. Hertzog, S.K. Krueger, Effects of exercise training versus attention on plasma B-type natriuretic peptide, 6-minute walk test and quality of life in individuals with heart failure, Cardiopulm. Phys. Ther. J. 23 (4) (Dec 2012) 19–25.
[19] D.M. Servantes, A. Pelcerman, X.M. Salvetti, A.F. Salles, P.F. de Albuquerque, F.C. de Salles, C. Lopes, M.T. de Mello, D.R. Almeida, J.A. Filho, Effects of home-based exercise training for patients with chronic heart failure and sleep apnoea: a randomized comparison of two different programmes, Clin. Rehabil. 26 (1) (Jan 2012) 45–57.
[20] A.L. Stevens, D. Hansen, L. Herbots, I. Wens, A. Creemers, P. Dendale, B.O. Eijnde, Exercise training improves insulin release during glucose tolerance testing in stable chronic heart failure patients, J. Cardiopulm. Rehabil. Prev. 35 (1) (Jan-Feb 2015) 37–46.
[21] H. JPT, T. S., J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analysis, Br. Med. J. 327 (7414) (2003) 557–560.
[22] T.B. Huedo-Medina, J. Sanchez-Meca, F. Marin-Martinez, J. Botella, Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol. Methods 11 (2) (Jun 2006) 193–206.
[23] M. Egger, G. Davey Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, BMJ 315 (7109) (Sep 13 1997) 629–634.
[24] N.A. Smart, W. M., H. Ismail, F. Giallauria, C. Vigorito, V. Cornelissen, G. Dieberg, Validation of a new tool for the assessment of study quality and reporting in exercise training studies: TESTEX, Int. J. Evid. Based Healthc. (2015) (In Press).
[25] R.S. Taylor, S. V., D. EJ, S. Briscoe, A.J.S. Coats, H. Dalal, F. Lough, K. Rees, S. Singh, Exercise-based rehabilitation for heart failure, Cochrane Database Syst. Rev. (2014).
[26] F.M. Sarullo, G. Fazio, I. Brusca, S. Fasullo, S. Paterna, P. Licata, G. Novo, S. Novo, P. Di Pasquale, Cardiopulmonary exercise testing in patients with chronic heart failure: prognostic comparison from peak VO_2 and VE/VCO_2 slope, Open Cardiovasc. Med. J. 4 (2010) 127–134.
[27] T.S. Rector, J.N. Cohn, Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group, Am. Heart J. 124 (4) (Oct 1992) 1017–1025.
[28] C.M. O'Connor, D.J. Whellan, K.L. Lee, S.J. Keteyian, L.S. Cooper, S.J. Ellis, E.S. Leifer, W.E. Kraus, D.W. Kitzman, J.A. Blumenthal, D.S. Rendall, N.H. Miller, J.L. Fleg, K.A. Schulman, R.S. McKelvie, F. Zannad, I.L. Pina, Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial, JAMA 301 (14) (Apr 8 2009) 1439–1450.
[29] M. Koch, H. Douard, J.P. Broustet, The benefit of graded physical exercise in chronic heart failure, Chest 101 (5 Suppl) (May 1992) 231S–235S.
[30] V.A. Cornelissen, R. Buys, N.A. Smart, Endurance exercise beneficially affects ambulatory blood pressure: a systematic review and meta-analysis, J. Hypertens. 31 (4) (Apr 2013) 639–648.
[31] U. Wisloff, A. Stoylen, J.P. Loennechen, M. Bruvold, O. Rognmo, P.M. Haram, A.E. Tjonna, J. Helgerud, S.A. Slordahl, S.J. Lee, V. Videm, A. Bye, G.L. Smith, S.M. Najjar, O. Ellingsen, T. Skjaerpe, Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study, Circulation 115 (24) (Jun 19 2007) 3086–3094.
[32] P.F. Cohn, R. Gorlin, M.V. Herman, E.H. Sonnenblick, H.R. Horn, L.H. Cohn, J.J. Collins Jr., Relation between contractile reserve and prognosis in patients with coronary artery disease and a depressed ejection fraction, Circulation 51 (3) (Mar 1975) 414–420.