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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 , cardio-myopathy and systolic heart dysfunction'.

Results The 27 included studies provided a total of 2,321 participants, 1,172 in an intervention and 1,149 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 $1.43 \text{ ml.kg}^{-1}.\text{min}^{-1}$ (95% CI 0.63, 2.23, $p=0.0004$); and in resistance vs control MD $3.99 \text{ ml.kg}^{-1}.\text{min}^{-1}$ (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 13.49m (95% CI $1.13, 25.84$, $p=0.03$); and resistance vs control MD 41.77m (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.

Keywords

Resistance training, combined training, heart failure

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 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.

Methods

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 scrutinised 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.

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 categorised 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.

Outcome measures

We recorded the following data; mortality, hospitalisations, 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.

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 (iii) we used default p values e.g. $p < 0.05$ becomes $p = 0.049$, $p < 0.01$ becomes $P = 0.0099$ and $p = \text{not significant}$ 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.

Statistical Analyses

Table 1. lists the meta-analyses conducted.

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).

Publication Bias

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

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 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.

Results

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 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, Figure 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, totalling 31,263 patient-hours of exercise training.

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 minutes. Details of the interventions in the included studies are detailed in Table 2.

Outcome Measures

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.

Hospitalisation

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.

Peak VO₂

Combined Aerobic and Resistance Exercise (CAR) vs. Control

Ten studies ($I^2=79\%$) were analyzed showing an improvement in Peak VO₂ in the combined groups MD of 1.43 ml.kg⁻¹.min⁻¹ (95% CI 0.63, 2.23, $p=0.0004$) Figure 2; SMD 0.73 (95% CI 0.22, 1.23, $p=0.005$).

Resistance exercise (RG) vs. Control

Four studies ($I^2=91\%$) were analyzed showing an improvement in Peak VO₂ in the resistance groups MD 3.99 ml.kg⁻¹.min⁻¹ (95% CI 1.47, 6.51, $p=0.002$) Figure 3; SMD 1.72 (95% CI 0.52, 2.93, $p=0.005$).

Combined Aerobic and Resistance (CAR) vs Aerobic

Six studies ($I^2=0\%$) showed no difference in peak VO₂ between combined and aerobic exercise groups, MD 0.61 ml.kg⁻¹.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, $p=0.08$),

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, $p=0.006$) Figure 4: SMD -0.32 (95%CI -0.58, -0.06, $p=0.01$).

LVEF%

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, $p=0.30$).

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, $p=0.88$).

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, $p=0.31$).

6-min walk test distance

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 13.49m (95% CI 1.13, 25.84, $p=0.03$) Figure 5; SMD 0.22 [95% CI -0.17, 0.60, $p=0.27$].

Resistance exercise (RG) vs. Control

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

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, $p=0.13$).

Peak Heart rate

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, $p=0.45$).

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, $p=0.005$) Figure 7; SMD 0.85 (95% CI 0.42, 1.28, $p<0.0001$).

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.

Publication Bias

Funnel (Egger) plots can be seen in the supplementary files, Figures S10-S24.. These analyses showed some evidence of publication bias.

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 2,300. 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 behaviour in terms of improving peak VO_2 . We should note that more than 4 ml.kg⁻¹.min⁻¹ improvement between resistance training versus control is a large effect size. This effect size is likely to elicit a number of favourable 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 from 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 tempers 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 2mmHg 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.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.min⁻¹ in resistance exercise versus control. This increase in peak heart rate would facilitate a small increase in peak cardiac output and peak VO₂. The increase in cardiac output

may result in improved contractile reserve which is associated with a more favourable prognosis in people with heart failure[32].

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.

Acknowledgements

None

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