International Journal of Cardiology 171 (2014) 62–65

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

# Exercise training program characteristics and magnitude of change in functional capacity of heart failure patients☆

Hashbullah Ismail, James R. McFarlane, Gudrun Dieberg, Neil A. Smart *

*School of Science and Technology, University of New England, Armidale, NSW 2351, Australia*

ARTICLE INFO

*Article history:*
Received 29 August 2013
Received in revised form 22 October 2013
Accepted 17 November 2013
Available online 22 November 2013

*Keywords:*
Exercise programming
Cardiorespiratory fitness
Heart failure
Meta-analysis

ABSTRACT

*Background:* Intuitively higher exercise program volume may be the primary stimulus for physical adaptation. We sought to establish if aerobic exercise training program characteristics produced different effect sizes for change in cardiorespiratory fitness in heart failure patients.

*Methods:* We conducted a MEDLINE search (1966 to 2012), for exercise based rehabilitation trials in heart failure, using the search terms 'exercise training, left ventricular dysfunction, peak $VO_2$, cardio-myopathy and systolic heart dysfunction'. Forty seven studies were included, producing 54 intervention groups; 3 (6%) were high-, 29 (54%) vigorous-, 20 (37%) moderate- and 2 (3%) low- intensity groups, providing a total of 2285 exercising subjects and 2098 control subjects, totaling 4383 participants.

*Results:* Peak $VO_2$ increased by a mean difference of 3.3 ml $kg^{-1}$ $min^{-1}$ [95% CI 0.53 to 6.13, $p = 0.02$] with high intensity training in exercise groups versus control, equating to a 23% improvement from baseline. The corresponding data for vigorous, moderate and low intensity were 8%, 13%; and 7% respectively. Weekly exercise energy expenditure >460 kcal was associated with a mean difference in peak $VO_2$ of 2.6 ml $kg^{-1}$ $min^{-1}$ [95% CI 1.88 to 3.28, $p < 0.00001$].

*Conclusions:* Our data suggest that high-intensity exercise, achieving at least 460 kcal weekly energy expenditure may elicit the greatest changes in cardiorespiratory fitness.



## 1. Introduction

Meta-analyses have shown exercise training to be beneficial in heart failure patients in terms of improved cardiorespiratory fitness [1,2]. Aerobic exercise probably produces the greatest improvements in peak $VO_2$ [2] and left ventricular ejection fraction [3]. Endothelial function [4] and serum levels of natriuretic peptides [5,6] and pro-inflammatory cytokines [7] are also improved with exercise training. The largest randomized trial of exercise training in heart failure to date [HF-ACTION] showed a modest effect on clinical endpoints [8]. The HF-ACTION trial was hindered by poor adherence in those allocated to exercise which may have led to the intervention group producing much smaller (4%) improvements in peak $VO_2$, than those expected [15%–17%] [2].

Recent work has shown high intensity interval exercise training to be superior for eliciting improvements in peak $VO_2$ and systolic heart function in heart failure patients [9,10], nevertheless other exercise program characteristics such as session duration, frequency or program duration may also explain the magnitude of change. Previous work has also suggested that intermittent exercise, albeit at high intensity, may produce optimal clinical improvements [10]. The underlying success of interval exercise may be that it allows for rest periods making it possible for patients with heart failure to perform all exercise at high intensity, possibly the major determinant of adaptation. However comparisons of intermittent and continuous exercise may be clouded by ambiguity over dose-responses [11]. Exercise session time required to complete the same volume of energy expended may be less for high intensity interval exercise than that of vigorous or moderate intensity exercise sessions [10 ]; in addition less frequent weekly attendance may be required of the patient. The resultant smaller time commitment is likely equated to better exercise adherence. For these reasons high intensity interval exercise has been suggested as a possible training prescription for heart failure patients [12].

We wished to identify which exercise program characteristics produce the largest improvements in peak $VO_2$. We therefore conducted a systematic analysis of all clinical randomized, controlled, aerobic exercise training trials in heart failure patients and stratified the trials by exercise intensity according to guidelines [13]. We aimed to compare various exercise program characteristics to see which produced larger effect sizes for change in peak $VO_2$ compared to sedentary controls. Second, we examined if rates of serious events, mortality and hospitalization were more frequent with any particular exercise program

☆ This work received no financial support and has no relationship to the industry.
* Corresponding author. Tel.: +61 2 6773 4076; fax: +61 2 6773 5011.
*E-mail address:* nsmart2@une.edu.au (N.A. Smart).

0167-5273/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijcard.2013.11.045

characteristics in heart failure patients. We hypothesized that higher training intensities were associated with larger changes in cardiorespiratory fitness. The focus of this work was placed upon aerobic exercise as resistance training (RT) studies tend not to use peak $VO_2$ as an outcome measure and there are insufficient isolated RT studies to warrant analyses. Moreover, existing RT studies seem to be comparisons of two or more exercise modalities, there are no sedentary comparator groups, rendering comparisons with controls impossible.

## 2. Methods

### 2.1. Search strategy

Studies were identified through a MEDLINE search (1985 to 2012), Cochrane Controlled Trials Registry (1966 to 2012), the manuscript 'exercise based rehabilitation for heart failure' review by the Cochrane Library (2010, Issue 4), CINAHL, SPORTDiscus and Science Citation Index. The search strategy included a mix of MeSH and free text terms for key concepts related to exercise training, left ventricular dysfunction, peak $VO_2$, cardio-myopathy and systolic heart dysfunction for clinical trials of exercise training in heart failure patients (see Supplementary Table 1 — search strategy). Studies were included if patients exhibited baseline left ventricular ejection fraction below 40%. These searches were limited to prospective randomized or controlled trials and human studies, and there were no restrictions on publication. Only English language papers were considered. Manuscript reference lists and latest journal editions were scrutinized for new references. Full articles were assessed by three reviewers (NS, GD and HI) for relevance and eligibility. Methodological disagreements were resolved by reviewer 4 (JF).

### 2.2. Study selection

Included were randomized controlled designs of exercise training in chronic heart failure patients that reported change in peak $VO_2$. Studies of heart failure patients with preserved ejection fraction (HFpEF) were excluded as we wished to avoid comparing different clinical populations and HFpEF patients would have made up a disproportionate (fewer) number of total patients. All included studies are comparisons between groups with different exercise intensities and/or control. Reviewers categorized the studies into four groups based on exercise intensity, described in a recent position stand by Exercise and Sport Science Australia [13]. All studies were categorized into high, vigorous, moderate or low exercise intensity based on details provided in manuscripts. The measures used to classify exercise intensity were percentage of Heart Rate Maximum ($\%HR_{max}$), heart rate reserve (%HRR), peak oxygen uptake (% $VO_2$ peak) and Borg score [13].

Records identified 222 papers through database searching. Twelve additional records from reference lists were added. Only principal studies, with the most subjects, were included where multiple publications existed from the same dataset. After initial screening, 108 studies were removed, which include over-lapping, duplicates, duplicate data, abstracts, irrelevant articles e.g. editorials and discussion papers. We further excluded 44 studies for the following reasons; the control group received additional intervention, non-relevant studies; studies using inspiratory muscle training and acute exercise responses and non-English manuscripts. Three studies were excluded as study authors failed to provide missing data; thirty two studies were excluded as they did not measure peak $VO_2$, leaving 47 studies for analysis (Supplementary Fig. 1 — consort statement).

### 2.3. Outcomes measures

We recorded the following: peak $VO_2$ (baseline and post exercise), training frequency, intensity, duration per session and length of program, participant completion rates and mortality. We chose to dichotomize the data according to median values, this resulted in comparisons as follows: weekly exercise frequency (<3 versus ≥3 weekly sessions); Session duration (<35 versus ≥35 min); program duration (<12 weeks versus ≥12 weeks); total exercise program volume energy expenditure (<4000 kcal versus ≥4000 kcal). See Supplementary Table 2 for details of included studies. The following variables were categorized according to previous recommendations [5,14]: weekly exercise energy expenditure (<460 kcal versus ≥460 kcal); exercise intensity was separated into four categories in line with a recently published guideline [13].

### 2.4. Data synthesis

We calculated energy expenditure by first calculating kilocalories consumed per minute during exercise by taking the percentage of peak $VO_2$ that corresponded to exercise training intensity and then using mean group body mass to convert to liters of oxygen utilized per minute. We then multiplied by a conversion rate of 5 kcal for every liter of oxygen used. The weekly exercise energy expenditure was the determined from the product of kilocalories consumed per minute, session duration and weekly session frequency. We calculated patient-hours of exercise training and percentage change in peak $VO_2$ and also performed an analysis of mortality and adverse events; see Supplementary Table 3.

### 2.5. Assessment of study quality

We assessed study quality using the PEDro scale [15] with slight modification as subject blinding is unlikely in exercise training studies, so maximum possible PEDro score was 8 (no mark is awarded for stipulating eligibility criteria; see Supplementary Table 4.

### 2.6. Statistical analyses

Revman 5.1 software (The Nordic Cochrane Centre, Copenhagen, Denmark) was used to construct forest plots. Continuous data were reported as mean and standard deviation. Revman 5.1 enabled calculation of post-intervention change from baseline for standard deviation, using change in mean values, number of subjects and $p$-value or preferably 95% confidence intervals. In many cases where exact $p$-values were not provided, we used default values e.g. $p < 0.05$ became $p = 0.049$. Mean difference (MD) in these data from baseline was analyzed. For dichotomous data such as difference between exercise and control participants for mortality, chi-squared analyses were performed. As hospitalizations fall as deaths increase, we also calculated a composite endpoint of death or hospitalization. We used a 5% level of significance and a 95% confidence interval to report change in outcome measures. Egger plots were produced to identify sources of publication bias [16]. We analyzed baseline versus post-intervention change in peak $VO_2$ for the stipulated exercise prescription categories.

## 3. Results

### 3.1. Included studies

Forty seven studies met selection criteria, totaling 54 exercise intervention groups, as seven studies included two training intervention groups (Supplementary Table 2). Of these, 3 (6%) were high-, 29 (54%) vigorous-, 20 (37%) moderate- and 2 (3%) low-intensity groups, providing a total of 2285 exercising subjects and 2098 control subjects, totaling 4383 participants. Of these, 58 patients completed high-intensity, 1765 vigorous-intensity, 423 moderate-intensity and 39 low-intensity training. Mean weekly exercise energy expenditure was 1030 ± 353 kcal for high-, 480 ± 233 kcal for vigorous-, 542 ± 357 kcal for moderate- and 380 ± 215 kcal for low-intensity training. These values were equated to high- (11.6 MET-hours), vigorous- (5.4 MET-hours), moderate- (6.1 MET-hours) and low-intensity (4.3 MET-hours) training respectively.

### 3.2. Peak $VO_2$

In terms of absolute change, peak $VO_2$ increased for high intensity exercise training with a mean difference (MD) of 3.3 ml $kg^{-1}$ $min^{-1}$ (95% CI, 0.53 to 6.13, $p = 0.02$); for vigorous intensity training with an MD of 2.3 ml $kg^{-1}$ $min^{-1}$ (95% CI, 1.70 to 2.84, $p < 0.00001$); for moderate intensity training with an MD of 2.2 ml $kg^{-1}$ $min^{-1}$ (95% CI, −1.39 to 2.99, $p < 0.00001$), and was not significant for low intensity exercise training (see Supplementary Figs. 2–5). Our analyses suggest that high intensity exercise provides an improvement from baseline of 23%. Total energy expenditure <4000 kcal produced improvements in peak $VO_2$ (MD) 2.0 ml $kg^{-1}$ $min^{-1}$ [95% CI 0.92, 3.03, $p = 0.0002$] very similar to programs >4000 kcal change in peak $VO_2$ (MD) 2.2 ml $kg^{-1}$ $min^{-1}$ [95% CI, 1.72, 2.59, $p < 0.00001$] (see Supplementary Figs. 6 and 7, respectively). Weekly exercise energy expenditure in excess of 460 kcal produced improvements in peak $VO_2$ (MD) of 2.6 ml $kg^{-1}$ $min^{-1}$ (95% CI 1.88 to 3.28, $p < 0.00001$), compared to programs expending <460 kcal weekly (see Supplementary Figs. 8 and 9 respectively). Session frequency <3 times per week produced MD of 2.3 ml $kg^{-1}$ $min^{-1}$ [95% CI, 1.76, 2.82, $p < 0.00001$] changes in peak $VO_2$, while >3 weekly sessions produced MD of 1.9 ml $kg^{-1}$ $min^{-1}$ [95% CI, 1.12, 2.63, $p < 0.00001$] (see Supplementary Figs. 10 and 11, respectively). Session duration of <35 min produced peak $VO_2$ improvement of MD of 2.1 ml $kg^{-1}$ $min^{-1}$ (95% CI, 1.52 to 2.69, $p < 0.00001$), while sessions of >35 min produced peak $VO_2$ improvement of MD of 2.3 ml $kg^{-1}$ $min^{-1}$ (95% CI, 1.65 to 2.97, $p < 0.00001$) (see Supplementary Figs. 12 and 13). Also of interest was that shorter program durations