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The influence of training characteristics on the effect of aerobic exercise training in patients with chronic heart failure: A meta-regression analysis☆

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ABSTRACT

Although aerobic exercise training has shown to be an effective treatment for chronic heart failure patients, there has been a debate about the design of training programs and which training characteristics are the strongest determinants of improvement in exercise capacity. Therefore, we performed a meta-regression analysis to determine a ranking of the individual effect of the training characteristics on the improvement in exercise capacity of an aerobic exercise training program in chronic heart failure patients. We focused on four training characteristics; session frequency, session duration, training intensity and program length, and their product; total energy expenditure. A systematic literature search was performed for randomized controlled trials comparing continuous aerobic exercise training with usual care. Seventeen unique articles were included in our analysis. Total energy expenditure appeared the only training characteristic with a significant effect on improvement in exercise capacity. However, the results were strongly dominated by one trial (HF-action trial), accounting for 90% of the total patient population and showing controversial results compared to other studies. A repeated analysis excluding the HF-action trial confirmed that the increase in exercise capacity is primarily determined by total energy expenditure, followed by session frequency, session duration and session intensity. These results suggest that the design of a training program requires high total energy expenditure as a main goal. Increases in training frequency and session duration appear to yield the largest improvement in exercise capacity.

1. Introduction

The beneficial effects of aerobic exercise training (AET) programs for chronic heart failure (CHF) patients have been demonstrated throughout the last decades [1,2]. However, training characteristics of exercise programs (i.e. training intensity, session duration, session frequency and program length) vary considerably between trials [3–6]. Although it is generally conceived that all of these characteristics influence training results in CHF patients, it remains unclear to what extent they determine the effect of AET separately. In recent years, training intensity has been a point of debate. In the first decade of the 21st century, most AET-trials studied training programs with low to moderate training intensity, showing mainly beneficial effects on exercise capacity [6,7]. Several smaller trials showed a greater improvement in exercise capacity, using a high training intensity [8,9]. However, trials directly comparing moderate and high intensity training programs showed conflicting results [3,10,11]. Moreover, in most of the studies comparing different intensities, high intensity exercise was performed as interval training, while the low to moderate intensity exercise group underwent continuous training. The pure effect of training intensity therefore remains clouded by the use of different training modalities. Besides training intensity, data on the influence of other training characteristics on exercise capacity in CHF patients (i.e. session duration, session frequency and program length) are scarce and therefore remains largely unclear. Available data consist of a substudy of the HF-action trial which showed that high training volume (product of session duration, session frequency and program length) was positively correlated with improvement of peakVO_2, and Vanhees et al. showing that session frequency can be an important determinant of training effects in CHF patients [12]. A recent meta-analysis on this topic suggested that high training intensity and high training volume elicit the greatest improvement in exercise capacity in CHF patients [13]. However, analyses were performed without adjustment for total energy expenditure of the training program. A correction for total energy expenditure, the product of session duration,

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session frequency, training intensity and program length, is required to identify the effect of the individual training characteristics.

The objective of this meta-regression analysis was to explore which program characteristics determine improvement in exercise capacity after exercise training in CHF patients, taking two constraints into consideration: 1) To identify the effect of the individual training characteristics, an adjustment for total energy expenditure was made in the analyses of session duration, session frequency, program length and training intensity. 2) To isolate the effect of training intensity, the analyses was focused on aerobic continuous training as training modality.

2. Methods

2.1. Literature search strategy

A search in both Medline and Embase was performed, for original articles written in English published between 1st of April 2007 to 1st of April 2015 and evaluating the effect of AET-programs on exercise capacity in CHF patients. The search strategy involved a mix of MeSH-terms and free text terms with synonyms on three different topics: population (i.e. heart failure, coronary artery disease, cardiac patients), therapy (i.e. cardiac rehabilitation, secondary prevention, physical training, exercise program) and outcome (i.e. exercise capacity, physical function, exercise tolerance). This search was combined with a search strategy to identify English written randomized controlled trials published between 01-04-2007 and 01-04-2015 and a search to limit for the correct diagnosis (i.e. not kidney failure, diabetes mellitus or obesity). The full electronic search strategy of the Medline database is described in Appendix A. The protocol of this meta-analysis was published in the Prospero database (http://www.crd.york.ac.uk/prospero) with registration number: CRD42014014846.

2.2. Study selection

Randomized controlled trials comparing continuous AET programs to usual care, using peakVO_2 to evaluate exercise capacity, were included. Studies evaluating resistance training, interval training or CR modalities not affecting exercise capacity (e.g., relaxation therapy, education, cognitive therapy) were excluded. To be able to properly compare different exercise protocols, only studies describing the AET protocol in terms of session duration, session frequency, program length and training intensity (% of peak heart rate, heart rate reserve, peakVO_2 or maximum workload) were included. To rule out the confounding influence of training modality on peakVO_2, studies that reported the results of a combination of aerobic exercise with strength training were excluded. When crucial data concerning the outcome parameter or training protocol was missing, authors were contacted to retrieve the missing data.

2.3. Data collection process

After the electronic searches, the abovementioned inclusion and exclusion criteria were used to screen all titles and abstracts in four groups of two researchers. Both researchers performed the screening independently, after which they compared the results and reached consensus. Of the selected articles, the full text was screened by three groups of two independent researchers to make the final decision on inclusion in a similar procedure. When no consensus was reached between two researchers, a third researcher decided whether the article was included or not. Data of included papers were extracted from full texts and stored in a Microsoft Access database through a form with predefined items describing study and patient characteristics, exercise protocol, outcome measurements and risk of bias assessment.

2.4. Energy expenditure

Energy expenditure in joules/kg ($J.kg^{-1}$) was calculated for every exercise intervention by multiplying training duration with training intensity. All training intensities were converted to a percentage of peakVO_2 using a conversion table from the American College of Sports Medicine [14]. Following this, training VO_2 in $ml.min^{-1}.kg^{-1}$ was calculated using the pre-training exercise capacity and training intensity and was multiplied with total program length of the exercise program in minutes. This resulted in total oxygen consumption in $ml.kg^{-1}$, which then was converted to $J.kg^{-1}$ using the equation of oxygen consumption and energy expenditure, according to the American College of Sport Medicine standards [14]. One liter of consumed oxygen is assumed to equal 5 kcal and one kilocalorie equals 4.186 J. Therefore, we assumed that 1 l consumed oxygen equals 20.93 J.

2.5. Risk of bias quality assessment

The methodological quality of each included article was assessed using the Cochrane Collaboration's tool for assessing risk of bias [15]. This tool identifies seven potential sources of bias in the design and conduct of randomized trials (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other forms of bias). An assessment requires that for each potential source of bias the risk is classified as 'low', 'high', or 'unclear', with the last category indicating either lack of information or uncertainty over the potential bias.

2.6. Synthesis of results

The relationship between the training characteristics and training-related changes in exercise capacity, expressed as peakVO_2, was determined using a meta-regression analysis. The effect of total energy expenditure was assessed using a univariate meta-regression. The effect of the four constituents of total energy expenditure (training intensity, session duration, session frequency and program length) was assessed by four multivariate meta-regressions, with total energy expenditure as a covariate. Model fit was assessed using residual deviance and the consistency parameter I^2, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). This is variability that would not be observed if all effect estimates were drawn from a single (unimodal) Gaussian distribution – large values of I^2 indicate inconsistency in the results of the underlying studies. The effect of training characteristics was assessed by their Z-score. Because of the large number of statistical comparisons, we considered p-values below 0.01 as significant. If there was evidence of inconsistency (i.e., I^2 was large) and there was sufficient data to estimate the heterogeneity parameter, the analysis was repeated without outliers. Baseline differences between groups were tested with an independent t-test using a significance level of 0.05.

3. Results

3.1. Study selection

The literature search identified 812 unique records from the MEDLINE and EMBASE databases. An overview of the search and selection of records is presented in Fig. 1. We excluded 593 records after screening of titles and abstracts and 187 records were excluded after full-paper review. From the remaining 32 records, 14 were included in an analysis for coronary artery disease patients and will be published elsewhere and 17 were included in this review. One of the included studies from Sandri et al. [16] stratified their participants in two intervention groups and two control groups based on age (i.e. ≤55 or ≥65). Therefore, we included this study as two separate comparisons.