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Long-term benefits of exercise training in patients with a systemic right ventricle

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ABSTRACT

Objectives: The aim of the present study is to determine the long-term effects of a ten-week exercise training program in adult patients with a systemic right ventricle.
Methods: All patients who participated in a 2009 randomized controlled trial were approached. At approximately three years of follow-up from initial baseline, patients underwent cardiopulmonary exercise testing, filled out two quality of life questionnaires, and NT proBNP levels were measured. All examinations were performed according to the protocols of the 2009 trial. In addition, patients were asked about their current sports habits.
Results: Of the 54 patients who were randomized in the 2009-trial 40 participated in the current re-evaluation (male 50%, ccTGA 35%, age 36 ± 10 years, intervention group n = 22, control group n = 18). After three years, no persistent effect of exercise training on $V'O_{2peak}$ training remained (−2% of predicted, 95% CI −3% to 5%; p = .56). However, patients who already participated in regular sports or exercise at baseline (n = 23/40 (58%)) showed higher $V'O_{2peak}$ of 13% of predicted (95% CI 4% to 23%; p > .01) and a decrease of 62% in plasma NT-proBNP (95% CI −115% to −10%; p > .03) during follow-up, when compared to patients who did not. Moreover, sports were associated with a lower incidence of clinical events (p = .032).
Conclusion: Short-term beneficial effects of exercise training did not persist over a three-year follow-up period. However, sports participation at baseline was associated with better exercise capacity, lower neurohormone levels, and increased event-free survival.

1. Introduction

The estimated prevalence of congenital heart disease (CHD) is 3 per 1000 live births, and the number of these patients that survive until adulthood is steadily increasing [1]. A substantial portion of these patients has a morphological right ventricle that sustains the systemic circulation, for instance patients with a transposition of the great arteries (TGA) after a Mustard or Senning operation, and patients with a congenitally corrected transposition of the great arteries (ccTGA). The large majority of adult patients with a systemic right ventricle is faced with deteriorating right ventricular function, and decreased exercise capacity [2].

In patients with acquired congestive heart failure the European Society of Cardiology recommends patient's participation in a multidisciplinary care program, which includes exercise training, to reduce the risk of heart failure hospitalization [3]. A study by O'Connor et al. showed an 11% reduction in all-cause mortality or all-cause hospitalization at 30 months of follow-up of a 3 month supervised training program, followed by a home-based training program [4]. In our own study, ten weeks of exercise training improved exercise capacity in patients with a systemic right ventricle [5]. In patients with acquired heart disease beneficial effects of exercise training are known to diminish as time from the training program progresses [6,7]. However, it remains unclear whether the effects of exercise training in adult patients with a systemic right ventricle is only temporary or whether it constitutes a permanent effect, possibly due to lifestyle changes. Therefore, the primary objective of this study is to determine the long-term effects of a ten-week exercise training program in adult patients with a systemic right ventricle.

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2. Methods

2.1. Study design

The present study was a one-time cross-sectional re-evaluation at three years follow-up of participants of the 2009 study "The effect of exercise in adult patients with a systemic right ventricle" (http://trialregister.nl id. NTR1909) [5].

2.2. Participants

All patients who participated in the 2009 study were eligible. These were adults with a systemic right ventricle due to congenitally or surgically corrected TGA. Patients who were mentally or physically incapable to participate in a home-based exercise program had been excluded, as were patients with experienced exercise-induced arrhythmia, symptomatic myocardial ischemia, a resting systolic blood pressure ≥200 mm Hg and/or diastolic blood pressure ≥110 mm Hg, New York Heart Association (NYHA) class III or IV, pregnancy during the training period, and non-cardiac co-morbidity that could affect exercise performance or that could aggravate by exercise.

2.3. Study settings

The study was conducted in the Netherlands (three sites) and Italy (one site). The study complies with the Declaration of Helsinki and was approved by the locally appointed Ethics Committee of all participating centers. Renewed informed consent was obtained from all participants prior to participation in the present re-evaluation.

2.4. Interventions

In 2009 consenting patients were randomized using unmarked opaque envelopes to an intervention group with three aerobics step training sessions per week for 10 consecutive weeks, and a control group. The detailed exercise training protocol has been published previously [5].

2.5. Sports participation

Patients were asked to indicate 1) whether they currently participated in sports or physical exercise, 2) how many times they participated in sports or exercise and 3) with what intensity (light, medium, heavy). The answers were compared to the data of the original trial. Patients who participated in sports or those who exercised at least 1 h weekly in an activity that scored 5 METS or more according to the Compendium of Physical Activities [8], were considered to be active in sports, while patients who scored below this threshold were not considered active in sports or exercise.

2.6. Outcomes

2.6.1. Cardiopulmonary exercise testing

Exercise testing was performed on an upright bicycle ergometer. After an initial calibration period of 2 min, workload was increased by 5–15 W/min in a stepwise manner. The exercise protocol was identical to the tests performed in 2009. Breath-by-breath analysis of minute ventilation, oxygen uptake ($V'O_2$), carbon dioxide elimination ($V'CO_2$), heart rate, blood pressure and electrocardiography was made.

2.6.2. Serum N-terminal pro-hormone of brain natriuretic peptide

Samples were analyzed locally and in a standardized fashion. N-terminal pro-hormone brain natriuretic peptide assessment kits differed between participating centers, although the same kit was used for the same patient.

2.6.3. Quality of life

Health-related quality of life was assessed by means of the Dutch and Italian translations of the Medical Outcomes Study Short Form 36 item (SF-36) health survey [5]. The SF-36 is a generic multi-item questionnaire comprising of 36 questions on eight domains (physical functioning, role functioning physical, bodily pain, general health perception, vitality, social functioning, role functioning emotional, and mental health). Scores range from 0 to 100, with higher scores representing better quality of life. Patients' SF-36 scores were analyzed in comparison to published age- and gender-matched reference population norms, after which the eight domains were combined into two higher ordered clusters; the physical component summary and the mental component summary.

In addition, the quality of life was assessed by means of the Dutch and Italian translations of the CHD-TNO/AZL Adult Quality of Life (CHD-TAAQOL) questionnaire [5]. The CHD-TAAQOL was developed as a disease specific tool for measuring health-related quality of life in adults with congenital heart defects. Scores were transformed to a 0–100 scale, with higher scores representing better quality of life.

2.6.4. Statistical analysis

Data are expressed as numbers with percentage, as mean with standard deviation, or median with interquartile range (IQR) as appropriate. Analysis was intention-to-treat. Chi-square and Students independent t-test were performed to evaluate whether the re-recruitment process might have imbalanced the study groups, the original grouping being the result of randomization. Changes from baseline in each group were evaluated using a two-tailed paired t-test or Wilcoxon matched pairs signed ranks test where appropriate. Significance and size of the treatment effect (intervention vs control) were determined by analysis of covariance. The analysis was adjusted for baseline values and participating center (to account for stratification). In addition, a sensitivity analysis including only those patients who completed the protocol in both 2009 and 2013 was performed. A 2-tailed p-value of <0.05 was used as a criterion for statistical significance.

2.7. Additional analyses

An exploratory multivariate analysis of covariance was performed to assess whether any determinants at baseline were associated with exercise capacity at follow-up. Moreover, a composite endpoint of clinical events was defined similar to a previous publication [9]. This included any arrhythmia, reoperation, thromboembolism, myocardial infarction, worsening heart failure, and death. Event-free survival was estimated using all available data (including chart review of non-participating patients). In patients with multiple events only the first event was used in survival analysis. Differences in the occurrence of complications were assessed using a log rank test.

3. Results

3.1. Recruitment

Between January and September 2013 all but 2 (one could not be reached, one had died) of the original 54 participants were contacted by telephone. Of the remaining 52 original study entrants who were contacted 12 did not consent to the full cardiopulmonary exercise test protocol (the primary outcome), citing no time and the distance to their tertiary referral center as the main reason. Of these 12 patients, 3 participated partly by filling out the quality of life questionnaires only. Consequently, 40 patients completed the full cardiopulmonary exercise test protocol. Of these 40 participants, 4 patients had not completed the full protocol in 2009 (Fig. 1). Consequently, 22 patients who were originally assigned to the intervention group and 18 patients who were assigned to the control group were analyzed in the assessment of the primary endpoint. There were no differences in baseline parameters (age, $V'O2_{peak}$, NT proBNP, medication, NYHA class) or event-rate between the 40 participants of the current follow-up study and the 14 non-participants. In 50 of the original 54 participants medical charts with complete follow-up were available leaving 50 patients for survival analysis.

3.2. Baseline data

Table 1 outlines the baseline characteristics of all patients who participated in the follow-up analysis. The study groups were reasonably well balanced at the present re-evaluation, although patients with Senning operation were overrepresented in the intervention group, without reaching statistical significance.

3.3. Outcomes and estimations

3.3.1. Cardiopulmonary exercise testing

In the overall group (n = 40), $V'O_{2peak}$ showed no significant change from baseline to three years of follow-up (−0.7 ml/kg/min 95% CI −2.6 ml/kg/min to 1.1 ml/kg/min, p = .43), nor were there significant changes in the two treatment groups (intervention 0.1 ml/kg/min 95%, CI −2.7 ml/kg/min to 2.8 ml/kg/min, p = .96; control −1.6 ml/kg/min, 95% CI −4.2 ml/kg/min to 0.9 ml/kg/min, p = .18). At three year follow-up, there were no differences in change in cardiopulmonary or hemodynamic parameters between the intervention and control groups (Table 2). A sensitivity analysis that included only patients who completed in the protocol in both 2009 and 2013 (control n = 15, intervention n = 21) yielded similar results ($V'O_{2peak}$ 1.8 mg/kg/min (−1.8 mg/kg/min to 5.5 mg/kg/min, p = .311)).

3.3.2. Sports habits

Patients in the intervention group were not more likely to change their exercise habits than patients in the control group (increase in habitual exercise: intervention 37% vs controls 24%, p = .38).