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REVIEW ARTICLE

Impact of Exercise Training in Aerobic Capacity and Pulmonary Function in Children and Adolescents After Congenital Heart Disease Surgery: A Systematic Review with Meta-analysis

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Abstract The aim of the study was to examine the effects of exercise training on aerobic capacity and pulmonary function in children and adolescents after congenital heart disease surgery. We searched MEDLINE, Cochrane Controlled Trials Register, EMBASE, (from the earliest date available to January 2015) for controlled trials that evaluated the effects of exercise training on aerobic capacity and pulmonary function (forced expiratory volume in 1 s and forced vital capacity) in children and adolescents after congenital heart disease surgery. Weighted mean differences and 95 % confidence intervals (CIs) were calculated,, and heterogeneity was assessed using the I^2 test. Eight trials ($n = 292$) met the study criteria. The results suggested that exercise training compared with control had a positive impact on peak VO_2. Exercise training resulted in improvement in peak VO_2 weighted mean difference (3.68 mL kg^{-1} min^{-1}, 95 % CI 1.58–5.78). The improvement in forced expiratory volume in 1 s and forced vital capacity after exercise training was not significant. Exercise training may improve peak VO_2 in children and adolescents after congenital heart disease surgery and should be considered for inclusion in cardiac rehabilitation. Further larger randomized controlled trials are urgently needed to investigate different types of exercise and its effects on the quality of life.

Keywords Exercise · Exercise test · Quality of life · Rehabilitation

Background

Over the past two decades, medical and surgical advances have dramatically increased the survival rates of children and adolescents with congenital heart disease (CHD) [5]. Despite the well-known positive effects of the surgery, low exercise capacity has been found to be an independent predictor of death or hospitalization for individuals with CHD [10, 30].

It is known that, after surgical procedure, exercise capacity is not restored to normal values. This low physical activity level and low exercise capacity are attributed to a combination of cardiopulmonary, muscular, and psychosocial limitations [7, 28].

Cardiac rehabilitation is growing in importance in the context of CHD. Data concerning the effect of exercise training in pediatric patients with CHD after cardiac surgery are now available. Although cardiac surgery is quite common in children, it is not yet known whether exercise is beneficial in restoring capacity to normal levels; moreover, the available studies have included small numbers of patients and show mixed results [3]. This scenario makes it difficult to establish recommendations about exercise training.

There is no doubt that exercise training is beneficial for adult patients after cardiac surgery [20]. However, meta-analyses have never been performed to investigate the effects of exercise training in children and adolescents after

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CHD surgery. Moreover, it is known that meta-analysis technique minimizes subjectivity by standardizing treatment effects of relevant studies into effect sizes (ESs), pooling the data, and then analyzing it to draw conclusions. The aim of this systematic review with meta-analysis was to analyze the published controlled trials that investigated the effects of postsurgical exercise training on exercise capacity and pulmonary function of children and adolescents after CHD surgery.

Methods

This meta-analysis was completed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24].

Eligibility Criteria

This systematic review included all controlled trials that studied the effects of exercise training in children and adolescents after CHD surgery. To be eligible, the trial should have children and/or adolescents after CHD surgery assigned to a group of exercise.

The tetralogy of Fallot, Senning/Mustard procedure (transposition of the great arteries), septum arterial surgery (correction of arterial septum and also the Fontan procedure (pulmonary valve atresia) were considered in this review.

The main outcomes of interest were peak oxygen consumption (peak VO_2, mL kg^{-1} min^{-1}), pulmonary function (FEV1 and FVC), muscle performance, oxygenation, and quality of life.

Search Methods for Identification of Studies

We searched MEDLINE, PEDro, EMBASE, SciELO, Cumulative Index to Nursing and Allied Health (CINAHL), and the Cochrane Library for relevant studies published up to January 2015 without language restrictions. A standard protocol for this search was developed, and whenever possible, controlled vocabulary (Mesh—Medical Subject Headings—term for MEDLINE and Cochrane and EMTREE for EMBASE) was used. Key words and their synonyms were used to sensitize the search.

For the identification of controlled trials in PubMed/MEDLINE, the optimally sensitive strategy developed for the Cochrane Collaboration was used [17]. To identify the controlled trials in EMBASE, a search strategy using similar terms was adopted. In the search strategy, there were three groups of keywords: study design, participants, and interventions.

The references of articles eligible for this systematic review were analyzed to detect other potentially eligible studies. For ongoing studies or when the confirmation of any data or additional information was needed, the authors were contacted by e-mail.

Data Collection and Analysis

The previously described search strategy was used to obtain titles and abstracts of studies that might be relevant for this review. Each abstract identified in the research was independently evaluated by two authors. If at least one of the authors considered one reference eligible, the full text was obtained for complete assessment. Two reviewers independently assessed the full text of selected articles to verify whether they met the criteria for inclusion or exclusion. A standardized data extraction form was used for inclusion and exclusion criteria.

Two authors independently extracted data from the published reports using standard data extraction forms adapted from the Cochrane Collaboration's [17] model for data extraction, considering the (1) aspects of the study population, such as the average age and sex; (2) aspects of the intervention performed (sample size, type of exercise performed, the presence of supervision, frequency, and duration of each session); (3) follow-up; (4) loss to follow-up; (5) outcome measures; and (6) presented results. Disagreements were resolved by one of the authors. Any further information required from the original author was requested by e-mail.

Quality of Meta-analysis Evidence

The quality of evidence generated by this systematic review was classified using the PEDro scale. The PEDro scale assesses the methodological quality of a study based on important criteria, such as concealed allocation, intention-to-treat analysis, and the adequacy of follow-up. These characteristics make the PEDro scale a useful tool for assessing the quality of physical therapy and rehabilitation trials [27].

Methodological quality was independently assessed by two researchers. Studies were scored on the PEDro scale based on a Delphi list [33] that consists of 11 items. One item on the PEDro scale (eligibility criteria) is related to external validity and is generally not used to calculate the method score, leaving a score range of 0–10 [19].

Statistical Assessment

Pooled effect estimates were obtained by comparing the least square mean percentage change from baseline to study end for each group, and were expressed as the weighted mean difference between groups. When the standard deviation (SD) of change was not available, the

SD of the baseline measure was used for the meta-analysis. Calculations were done using a random effects model. One comparison was made: exercise versus control group (non-exercise). And a value of 0.05 was considered significant. Statistical heterogeneity of the treatment effect among studies was assessed using Cochran's Q test and the inconsistency I^2 test, in which values between 25 and 50 % were considered indicative of moderate heterogeneity, and values >50 % were considered indicative of high heterogeneity [18]. All analyses were conducted using Review Manager version 5.0 (Cochrane Collaboration) [6].

Results

Description of Selected Studies

The initial search led to the identification of 83 abstracts, from which 12 were considered as potentially relevant and retrieved for detailed analysis. Only eight papers [2, 12, 13, 16, 22, 23, 29, 31] met our eligibility criteria. Figure 1 shows the PRISMA flow diagram of studies in this review.

The remaining eight articles were fully analyzed and approved by both reviewers and had the extraction of data from each controlled trial. Each of the papers was assessed using the PEDro scale methodology by both reviewers. The results of the assessment of the PEDro scale are presented individually in Table 1.

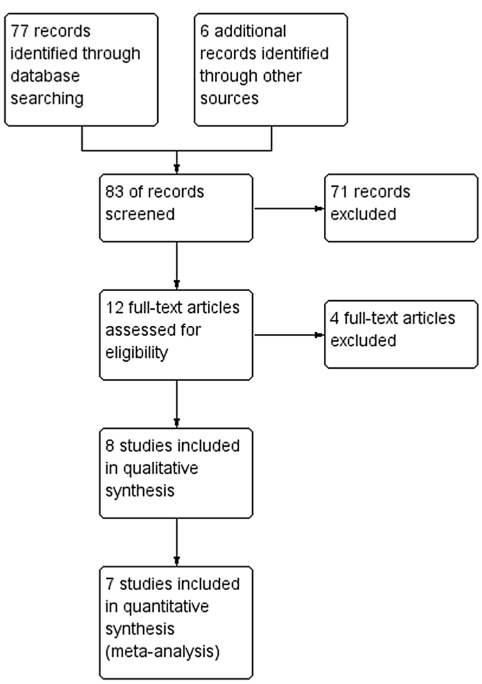


Fig. 1 Search and selection of studies for systematic review according to PRISMA

Study Characteristics

The final study samples ranged from 14 [31] to 83 [16], and mean age of participants ranged from 11 to 16 years. Studies included both genders, but there was a predominance of male participants. All studies analyzed in this review included outpatients; children and adolescents after CHD surgery (right ventricular outflow tract reconstruction for tetralogy of Fallot, transposition of the great arteries (Senning/Mustard procedure); atrial septal defect correction (suture closure); and pulmonary valve atresia (Fontan procedure). Table 2 summarizes the participants included, sample size, outcomes, and results of included studies.

Outcomes of Included Studies

Peak VO_2 was assessed in five studies [2, 16, 22, 29, 31]. The studies by Singh et al. [31], Rhodes et al. [29], Moalla et al. [22], and Amiard et al. [2] used a cycloergometer, and the study by Fredriksen et al. [16] used a treadmill. Spirometric measurements were taken in the studies by Rhodes et al. [29] and Moalla et al. [22] which included the forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC). Results were expressed as absolute values or as a percentage of predicted reference values (% pred). Isometric strength and endurance of the knee extensor muscles were measured by isokinetic dynamometer in the study by Moalla et al. [23]. Muscle strength corresponded to maximal voluntary contraction. Quality of life was measured in just one study [13] by the TNO/AZL Child Quality of Life Questionnaire, Child Form, and Parent Form.

Characteristics of Intervention Programs

The parameters used in the application of exercise were reported in the studies. The duration of exercise programs ranged from 8 [2] to 15 [16] weeks. Regarding the time of the session, there was a variation from 45 [22] to 60 [2, 12, 22, 23, 29, 31] min. The frequency of sessions ranged from 2 to 3 times a week. The intensity of exercise training was adjusted by peak VO_2, heart rate, and dyspnea threshold. The exercise intervention characteristics are provided in Table 3.

Peak VO_2

Five studies assessed peak VO_2 as outcome [2, 16, 22, 29, 31]. The meta-analyses showed (Fig. 2) a significant improvement in peak VO_2 of 3.68 mL kg^{-1} min^{-1} (95 % CI 1.58–5.78, $n = 196$) for participants in the exercise

Table 1 Study quality on the PEDro scale

	Study	1[a]	2	3	4	5	6	7	8	9	10	11	Total
1	Dulfer et al. [12]	✔	✔		✔				✔	✔	✔	✔	7
2	Moalla et al. [23]	✔	✔		✔						✔	✔	4
3	Singh et al. [31]	✔							✔	✔	✔	✔	5
4	Rhodes et al. [29]		✔		✔				✔	✔	✔	✔	7
5	Moalla et al. [22]	✔	✔	✔	✔				✔	✔	✔	✔	8
6	Amiard et al. [2]	✔							✔	✔	✔	✔	5
7	Fredriksen et al. [16]		✔	✔	✔				✔	✔	✔	✔	8
8	Dulfer et al. [13]		✔	✔	✔				✔		✔	✔	6

1 Eligibility criteria and source of participants, *2* random allocation, *3* concealed allocation, *4* baseline comparability, *5* blinded participants, *6* blinded therapists, *7* blind assessors, *8* adequate follow-up, *9* intention-to-treat analysis, *10* between-group comparisons, *11* point estimates and variability

[a] Item 1 does not contribute to the total score

Table 2 Characteristics of the included studies

	Study	Patients (diagnosis, *n* randomized, *n* analyzed, age, gender)	Intervention groups		Outcome measures	Results
			Treatment	Control		
1	Dulfer et al. [12]	CHD children (TF, FC), 71 randomized, 53 analyzed, 15.3 years, 70 % male	Aerobic and lightweight/ resistance exercises	Usual care	Psychological assessment	Exercise program had no effect on psychological outcomes in adolescents
2	Moalla et al. [23]	CHD children (TF, TGA, ASD, PA) 20 randomized, 18 analyzed, 12.9 years	Brisk walking/ jogging/running/ bicycle exercises/dynamic play	Usual care	Muscle oxygenation MVC CPET	Exercise training improves PMF by enhancing strength and endurance performance in children
3	Singh et al. [31]	CHD children (FC), 14 randomized, 14 analyzed, 12.1 years	Stationary bicycle	Usual care	CPET HR recovery	HR recovery following peak exercise improves in after exercise training
4	Rhodes et al. [29]	CHD children (OHS), 33 randomized, 33 analyzed, 12.0 years	Games/rubber balls/music	Usual care	CHQ CPET	Exercise training produces significant improvements in exercise function, self-esteem, and emotional state
5	Moalla et al. [22]	CHD children (TF, TGA, ASD, PA) 18 randomized, 18 analyzed, 12.9 years	Stationary bicycle	Usual care	Pulmonary ventilation CPET	Physical training at submaximal intensity induces better aerobic fitness and improves RMO
6	Amiard et al. [2]	CHD children (TF, PA, TGA, ASD) 23 randomized, 23 analyzed, 15 years, 56 % male	Swimming/football volleyball/skiing, cross-country skiing hiking	Usual care	CPET	Individualized training at VT improves, albeit nonsignificantly, aerobic capacity
7	Fredriksen et al. [16]	CHD children (TF, PA, TGA, ASD), 83 randomized, 83 analyzed, 12.4 years	Interval-training program	Usual care	Psychosocial factors CPET	The psychosocial scales showed a decrease in internalizing scores for those subjected to intervention
8	Dulfer et al. [13]	CHD children (TF, FC), 91 randomized, 50 analyzed, 15.3 years, 71.2 % male	Brisk walking/ jogging/running/ bicycle exercises/dynamic play	Usual care and continued their normal daily lives	HRQOL	Significant group differences in favor of exercise in HRQOL

CHD congenital heart disease, *TF* tetralogy of Fallot, *FC* Fontan circulation, *TGA* transposition of the great arteries, *ASD* atrial septal defect, *PA* pulmonary atresia, *OHS* open heart surgery, *PMF* peripheral muscular function, *MVC* maximal voluntary contraction, *CPET* cardiopulmonary exercise test, *CHQ* Child Health Questionnaire, *RMO* respiratory muscle oxygenation

Table 3 Characteristics of the experimental intervention in the trials included in the review

	Study	Modality	Intensity/duration (weeks)	Volume	Frequency (×per week)	Time (min)	Length (weeks)	Supervision
1	Dulfer et al. [12]	Brisk walking/jogging/running/bicycle exercises/dynamic play	60–70 % HR resting	10-min warm up 40-min aerobic training 10-min cool down	3	60	12	Yes
2	Moalla et al. [23]	Stationary bicycle	HR equal VAT	10-min warm up 45-min exercise 5-min cool down	3	60	12	Yes
3	Singh et al. [31]	Aerobic and lightweight/resistance exercises	peak VO_2 <80 %	5- to 10-min stretch 45-min exercise 5- to 10-min cool down	2	60	12	Yes
4	Rhodes et al. [29]	Games/rubber balls/music	HR equal VAT	5- to 10-min stretch 45-min exercise 5- to 10-min cool down	2	60	12	Yes
5	Moalla et al. [22]	Stationary bicycle	HR equal VAT	10-min warm up 45-min exercise 5-min cool down	3	60	12	Yes
6	Amiard et al. [2]	Interval-training program	Dyspnea threshold (±5 b/m)	10-min warm up 45-min exercise 5-min stretch	3	45	8	No
7	Fredriksen et al. [16]	Swimming/football volleyball/skiing, cross-country skiing hiking	65–80 % HR max	NI	2	NI	15	Yes
8	Dulfer et al. [13]	Brisk walking/jogging/running/bicycle exercises/dynamic play	60–70 % HR resting	10-min warm up 40-min aerobic training 10-min cool down	3	60	12	Yes

HR heart rate, *VAT* ventilatory anaerobic threshold, *NI* not informed

training group compared with non-exercising control group.

Pulmonary Function Tests

Two studies measured FEV1 and FVC [22, 29]. A non-significative improvement in FEV1 of 4.00 % pred (95 % CI −3.95 to 11.94, $n = 51$) was found for participants in the exercise group compared with control (Fig. 3a) A nonsignificative improvement in FVC of 3.51 % pred (95 % CI −3.95 to 11.94, $n = 51$) was also found for participants in the exercise group compared with control (Fig. 3b).

Quality of Life

Only one study assessed quality of life as an outcome [2]. This study compared the quality of life of children aged 10–15 years that were assigned to exercise training or control. The exercise group improved significantly on self-reported cognitive functioning, $p < 0.05$, and parent-reported social functioning, $p < 0.05$.

Muscle Oxygenation Changes

Only the study by Moalla et al. [22] described the oxygenation of the respiratory muscles (RMO2) as outcome. No significant difference was found between the initial tests of the control group and training group. The pattern of oxygenation in the control group was unchanged after 12 weeks, where progressive changes were noted in training group. Significant differences were found from 60 % VO_2 max until the end of exercise between pre- and post-training in the training group ($p < 0.01$) which indicated an improvement of tissue oxygenation.

Muscle Performance

Only the study by Moalla et al. [23] assessed isometric strength and endurance of the knee extensor muscles through an isokinetic dynamometer (Cybex Norm II).

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Amiard et al, 2008	3	9.9	13	1.6	14.4	10	4.1%	1.40 [-9.02, 11.82]
Fredriksen et al, 2000	1	8.2	55	-0.4	9.2	38	33.2%	1.40 [-2.24, 5.04]
Moalla et al, 2006	2.5	6.2	10	-0.3	7.2	8	11.1%	2.80 [-3.50, 9.10]
Rhodes et al, 2006	5.4	6	15	-0.6	4.2	18	33.9%	6.00 [2.40, 9.60]
Singh et al, 2007	4.9	7.5	14	0.3	6.1	15	17.7%	4.60 [-0.40, 9.60]
Total (95% CI)			**107**			**89**	**100.0%**	**3.68 [1.58, 5.78]**

Heterogeneity: Tau² = 0.00; Chi² = 3.49, df = 4 (P = 0.48); I² = 0%
Test for overall effect: Z = 3.44 (P = 0.0006)

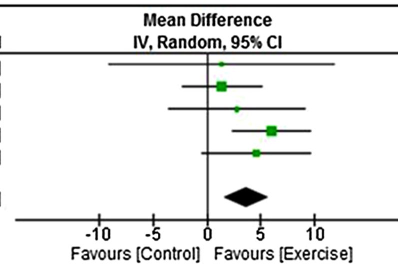


Fig. 2 Exercise training versus controls: VO_2 peak. Review Manager (RevMan) version 5.2 (Cochrane Collaboration), 2013

Muscle strength corresponded to maximal voluntary contraction, and muscle endurance corresponded to time to exhaustion or limit time (Tlim) at 50 % of maximal voluntary contraction. Exercise training group showed significant differences between pre- and post-training measurements, respectively, for both maximal voluntary contraction (101.6 ± 14.0 vs. 120.2 ± 19.4 N m, $p < 0.01$) and Tlim (66.2 ± 22.6 vs. 86.0 ± 23.0 s, $p < 0.01$), with no changes for controls.

Discussion

The main result of our systematic review and meta-analysis shows that exercise training was effective in increasing peak VO_2 in children and adolescents after CHD surgery. On the other hand, exercise training was not efficient in improving ventilatory variables (FVC and FEV1).

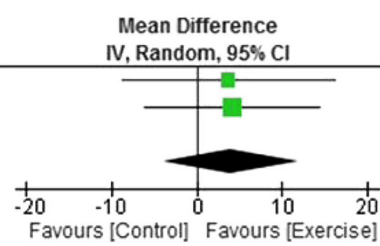
Exercise training is a well-established and important non-pharmacologic therapy in adult patients with heart diseases and is endorsed by the main guidelines around the world [1, 8]. However, exercise training in children and adolescents after CHD surgery is still little explored. Despite some available studies, we were unable to find any meta-analysis evaluating the exercise training in children and adolescents after CHD surgery. This systematic review with meta-analysis is important because it analyzes the exercise training as a potential co-adjuvant modality in cardiovascular rehabilitation of children and adolescents after CHD surgery. Moreover, the use of peak VO_2 as outcome in this meta-analysis is important because it is related to prognosis in patients with CHD [9, 26].

In the present review, one of the included studies did not report blind allocation or randomization in an appropriate way. Despite this, in our meta-analysis, the mean of peak VO_2 in the analyzed studies was 31.02 mL kg^{-1} min^{-1} at baseline, being 34.4 mL kg^{-1} min^{-1} at the end of the intervention, which represented an improvement of 13 % in peak VO_2 in the exercise group. Still considering peak VO_2, it is known that improvements above 10 % after

A

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Moalla et al, 2006	3.4	10.2	10	-0.3	15.5	8	40.6%	3.70 [-8.76, 16.16]
Rhodes et al, 2006	3.4	18.8	15	-0.8	8.6	18	59.4%	4.20 [-6.11, 14.51]
Total (95% CI)			**25**			**26**	**100.0%**	**4.00 [-3.95, 11.94]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.99 (P = 0.32)



B

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Moalla et al, 2006	2.4	5.8	10	0.2	15.1	8	47.6%	2.20 [-8.86, 13.26]
Rhodes et al, 2006	4.6	19.3	15	-0.1	8.6	18	52.4%	4.70 [-5.84, 15.24]
Total (95% CI)			**25**			**26**	**100.0%**	**3.51 [-4.12, 11.14]**

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)

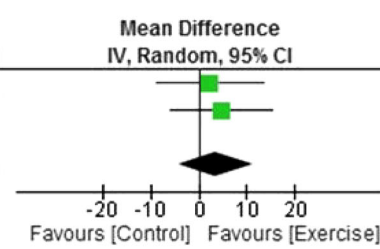


Fig. 3 Exercise training versus controls: FEV1 and FVC. Review Manager (RevMan) version 5.2 (Cochrane Collaboration), 2013. **a** Change in FEV1 and **b** change in FVC

cardiovascular rehabilitation programs are satisfactory and represent a good prognosis in adult patients with cardiac disease [15].

Children and adolescents with CHD have significantly lower quality of life than healthy controls [21]. Quality of life is a very important outcome in studies involving exercise training and heart diseases [13]. However, a meta-analysis was not possible in this study. We only found one RCT that investigated the effects of exercise training in children and adolescents after CHD surgery.

It has been reported that patients with CHD show a progressive, but slow, decline in exercise capacity [25]. Moreover, peak VO_2 is also an important prognostic variable that is associated with quality of life in patients with CHD [11, 13]. This prognostic variable creates a great expectation on the potential effects of exercise training in children and adolescents after CHD surgery. Despite this, only few studies are available, and our systematic review showed that exercise training improves peak VO_2. Unfortunately, no data are available about the influence of rehabilitation in survival of children and adolescents after CHD surgery.

The results of this review are in accordance with the findings of previous systematic reviews on exercise training in children and young adults with CHD. The authors concluded that exercise improved aerobic capacity in children and young adults with CHD [14]. However, this previous review included trials only up to 2012, and also included cohort studies and case report, and a meta-analysis was not performed. Meta-analysis technique minimizes subjectivity by standardizing treatment effects of relevant studies into effect sizes (ESs), pooling the data, and then analyzing it to draw conclusions.

Another systematic review in pediatric cardiac rehabilitation [32] describes that aerobic and resistance training were the core component of most studies, what is in accordance with our review. As well as in the review by Dupenn et al. [14], the authors included uncontrolled trials, making difficult a recommendation more accurate about exercise training in children and adolescents after CHD surgery.

Brassard et al. [4] published a review on exercise capacity and investigated the impact of exercise training in children and adolescents after Fontan procedure. This author concluded that exercise training had a beneficial effect on several parameters related to exercise tolerance. Three studies in our review included patients after Fontan procedure. One of them assessed the impact of exercise on aerobic capacity and confirmed that peak VO_2, 1-min heart rate recovery, and 3-min recovery improved significantly in exercise training group.

It is difficult to make a definitive recommendation about exercise training in children and adolescents after CHD surgery. Our search strategy only found few studies, and they were not uniform regarding the etiology of CHD and surgical procedures. Despite this, exercise training seems to be an important strategy to improve peak VO_2 in children and adolescents after CHD surgery and deserves more investigation with well-controlled RCTs.

Caution is warranted when interpreting our results given the small amount of studies and the significant heterogeneity found in the primary analyses. Further investigation is required to investigate how to sustain positive effects of exercise training in children and adolescents after CHD surgery.

Considering the low quality of the selected studies, additional well-controlled randomized controlled trials are required to strengthen the conclusion that of exercise training as an important non-pharmacologic treatment in children and adolescents after CHD surgery. It is important to determine the most appropriated methods (mode, intensity, frequency, duration, and timing) to achieve the best results regarding peak VO_2 and quality of life in pediatric rehabilitation. Moreover, the influence of exercise training in survival and re-hospitalization rates is a very important issue that must be considered in future investigations.

Conclusion

Taking in account the available studies, this systematic review showed that the exercise training should be considered as efficient method of improving peak VO_2 in children and adolescents after CHD surgery. Exercise training should be considered as a non-pharmacologic treatment for children and adolescents after CHD surgery.

Compliance with Ethical Standards

Conflict of interest None.

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