Heart, Lung and Circulation (2015) **24,** 753–768
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2015.03.005

REVIEW

Should We Recommend Exercise after the Fontan Procedure?

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Received 22 January 2015; accepted 3 March 2015; online published-ahead-of-print 24 March 2015

Background The Fontan procedure, the last of a series of operations performed in patients with congenital heart defects, offers improved exercise capacity compared to baseline function but is still reduced compared to healthy peers. Exercise training may improve exercise tolerance but there is no consensus on the safety of this practice or the optimal training regimen. We performed a systematic literature review on the effects of exercise training in patients with a Fontan circulation.

Methods Medline and Embase databases were systematically searched for articles regarding Fontan Procedure and cardiac rehabilitation.

Results A total of 23 articles met all inclusion criteria; in total, 201 Fontan subjects were included. Characteristics of the exercise training programs varied significantly. There were no adverse effects related to training programs reported in the literature. Most studies reported benefit across various exercise parameters related to exercise tolerance.

Conclusions Exercise training is safe and beneficial in patients with a Fontan circulation. Exercise training should become a standard of care within this population. Physiological adaptation following exercise training needs to be investigated more extensively.

Keywords Fontan procedure • Exercise therapy • Rehabilitation • Resistance training • Congenital heart disease • Safety

Introduction

The Fontan procedure is the last of a series of operations performed for patients with a single ventricle or those who cannot be offered a bi-ventricular repair. Today the Australia and New Zealand Fontan Registry, recording the clinical outcomes of all those undergoing Fontan surgery in the two countries, has identified more than 1200 patients alive with a Fontan circulation [1]. The procedure has resulted in improvements of long-term outcomes and it is hoped today that the majority of them will survive for at least 30 years after the procedure with a good quality of life [2]. In the Fontan circulation, the systemic venous blood flows passively through the lungs without being pumped by a right ventricle. The passive passage of blood through the lungs is made possible by the existence of elevated central venous pressure. The ventilatory pump augments flow through increased venous return during inspiration [3–6]. This unconventional circulation results in improved exercise capacity after Fontan surgery. Driscoll et al. observed a 16% increase (20.5ml/kg/min to 24.3ml/kg/min (p=0.001)) in peak oxygen consumption [7] after the Fontan procedure. Driscoll et al.'s

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result was later replicated by Zellers et al. [8] who reported a 19% increase in peak oxygen consumption following the Fontan procedure. These clinical trials confirmed that the Fontan procedure significantly increased subjects' peak work performance and duration of exercise compared to their preoperative function. Patients with a Fontan circulation who are dependent on the ejection of both the systemic and the pulmonary circulation in series by a single ventricle remain limited in their physical abilities with maximum oxygen consumption ranging from 48%-65% of predicted value compared to their peers [7,9–12].

Recent studies have demonstrated the mechanisms by which patients with Fontan circulation have a restricted exercise capacity [9,12–15]. The failure to increase stroke volume [12,14,15] seems to be at the core of the lack of capacity to increase cardiac output above a limited threshold [9,16]. The impaired stroke volume is a result of reduced preload caused by the lack of subpulmonary pump preventing direct increase in pulmonary blood flow [16,17]. Reduced arterial blood saturation and chronotropic impairment are minor centrally mediated mechanisms that may also contribute to the reduced peak oxygen consumption [9].

It is becoming apparent that the neglected peripherally mediated factors are an important influence on exercise tolerance, as the central cardiovascular factors only account for approximately 50% of the variance in anaerobic threshold and physical working capacity [16]. Remarkably, Cordina et al. recently established the correlation between increased muscle mass and increased peak oxygen consumption [21]. A striking 25% of Fontan subjects had severely reduced muscle mass. This muscle mass deficiency was also associated with impaired muscle aerobic capacity providing further evidence for the functional deficiency of the muscle in Fontan subjects compared with healthy controls. Additional to the diminished aerobic capacity, the majority of children with Fontan circulation failed to achieve current physical activity recommendations for children and adolescents [18]. Multiple factors across the social and psychological domains may influence their activity levels. These include perceived restrictions, due to overprotection from parents, with greater than 50% of children with congenital heart disease remarking that their parents limit their physical activities [19]. Higher levels of overprotection are associated with greater levels of heart-focussed anxiety [20].

Importantly, Cordina et al's. most significant achievement demonstrated that after 20 weeks of high-intensity resistance training peak oxygen consumption increased by 183ml/min associated with a 43% and 1.94 kg increase in muscle strength and total muscle mass respectively.

It is therefore becoming obvious that a regular exercise training program should be highly recommended to patients with a Fontan circulation. There is however, no clear consensus on the safety of this practice. The type and extent of exercise practices to be recommended are even more diverse. We decided to review the literature to identify the safety of exercise rehabilitation in Fontan patients and investigate whether recommendation of the type of exercise training could be drawn.

Method

Medline and Embase databases were used to search for articles from 1971 and September 2014 regarding the Fontan Procedure and cardiac rehabilitation utilising MeSH terms. The first search term used was: Fontan Procedure OR heart defect, congenital. The second search term was: exercise therapy OR exercise OR rehabilitation OR resistance training. Five hundred and four articles were identified. Twenty-three articles met the inclusion criteria requiring the study to incorporate exercise/training/rehabilitation in a population that included subjects with a Fontan circulation. The authors, study design, participants' age, number of participants, dropouts and excluded results, the inclusion and exclusion criteria, the outcome measures and outcomes including adverse sequelae and follow-up were extracted. In addition, the following data was collected about the characteristics of the rehabilitation program: setting, type of exercises, duration, frequency, intensity, monitoring and compliance if it was measured.

Results

The study design and population information is summarised in Table 1. Eight studies took place in a hospital setting [19,21–28], six were conducted in the home [29–35], two took place in a combination of hospital and home and four studies took place in supervised gyms [36–39]. The programs involved a number of different interventions with seven utilising aerobic training only [28,29,31–34,39,40] whilst two studies incorporated education and aerobic training [21,37]. Seven studies intervened with a combination of aerobic and resistance training [19,22–27,41]. The study by Cordina et al. is the only one that investigated the effect of resistance training alone [36]. Longmuir et al.s' intervention involved a fitness and motor skill development program and was compared to an education only control arm [30]. Morrison et al. studied the effect of motivational interviewing in combination with a monthly exercise plan [35] whilst Muller et al. investigated the effect of playful exercise [38]. The characteristics of the respective cardiac rehabilitation programs including frequency, duration and intensity of training are described in Table 2.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for respective studies are reviewed in Table 3. The inclusion criteria were not reported in two studies [21,29], whilst the exclusion criteria were not reported in three studies [21,28,39]. The remaining literature utilised varied criteria. Seven studies shared inclusion criteria of geographical proximity [28,31,36,37,39,41] whilst 11 studies applied the exclusion criteria or pre-existing condition that would prevent or influence exercise testing or training [24,27,30,32–34,36–38,40,41].

Table 1 Description of study design, populations and Fontan subjects.

Author	Date	Study Design NHMRC Classification	Total participants	Ages (yrs) (range/mean)	No. of Fontan Participants/total - Fontan only or heterogeneous	Intervention (Fontan/Total)	Control (Fontan/Total)	Drop-out - total [Pt/controls] (% of all participants)
Longmuir [30]	2013	Randomised controlled trial*	61	6-11/9.1	61/61– Fontan only	30/30 Activity	31/31 Education *	6 [1/5] (9.8%)
Brassard [41]	2006	Non-randomised experimental trial*	9	11-26/16±5	9/9- Fontan only	4/4	5/5 *	-
Cordina [36]	2013	Non-randomised experimental trial*	16	32±4 (SEM)	16/16- Fontan only	9/9	7/7 *	5 [3/2] (31.25%)
Minamisawa [31]	2001	Case series	13	13-25/19±4	13/13– Fontan only	13/13	-	2 [–] (15.4%) [did not complete training program]
Opocher [40]	2005	Case series	10	7-12/8.7±0.6	10/10 – Fontan only	10/10	-	0
McCall [25]	2001	Case report	1	18	1/1 – Fontan only	1/1	-	n/a
Lichtman [22]	2008	Case report	1	28	1/1 – Fontan only	1/1	-	n/a
Balfour [21]	1991	Case series	16	13.5-19.8/17.3±9	2/16 – Heterogeneous	2/16	-	9 [–] (56.25%)
Dua [29]	2010	Cohort study	61	18-63	3/61 – Heterogeneous	3/50 Subgroups (NYHA class) Grp1 – 1/21 Grp2 – 0/16 Grp 3- 2/13	-	11/0 (18%)
Fredriksen [37]	2000	Non-randomised experimental trial*	129	10-16	6/93 – Heterogeneous	4/55	2/38 *	36 [–] (27%) – Excluded if did not complete both questionnaires and CPET or training program. No description of which group they participated in.
Martinez-Quintana [23]	2010	Non-randomised experimental trial*	8	19-38/27.75±7.9	4/8 – Heterogeneous (all had pulmonary HTN)	2/4	2/4*	0
Moalla 2006 [34]	2006	Randomised controlled trial	18[$]	12-15	4/18 – Heterogeneous	2/10 (20%)	2/8 (25%)*	0
Moalla 2012 [32]	2012	Randomised controlled trial*	18[$]	12-15/13±1.4	4/18 – Heterogeneous	2/10 (20%)	2/8 (25%)*	0

Table 1. (continued)

Author	Date	Study Design NHMRC Classification	Total participants	Ages (yrs) (range/mean)	No. of Fontan Participants/total - Fontan only or heterogeneous	Intervention (Fontan/Total)	Control (Fontan/Total)	Drop-out - total [Pt/controls] (% of all participants)
Moalla 2005 [33]	2005	Randomised controlled trial*	17	12-14	4/17 – Heterogeneous	-/9^	-/8*^	0
Morrison [35]	2013	Randomised controlled trial*	143	12-20/15.6±2.27	13/143^ – Heterogeneous	-/72^	-/71*^	42 [10/32] (29.4%)
Rhodes 2005 [26]	2005	Case series	19	8-16/11.9±2.1	11/16 – Heterogeneous	11/16	-	3 (15.8%)
Rhodes 2006 [19]	2006	Non-randomised experimental trial*	33#	8-16/11.9±2.2	25/33 – Heterogeneous	11/15	14/18*	0
Ruttenberg [39]	1983	Non-randomised experimental trial§	24	7-18/12.9±3.5	2/24 – Heterogeneous	2/24	0/26§	39 [12/17] (58%) 1 Fontan drop-out
Singh [27]	2006	Non-randomised experimental trial*	29	-/12±1.8	24/29 - Heterogeneous	11/14	13/15*	-
Muller [38]	2013	Case series	14	4-6.1/4.7±0.6	1/14 - Heterogeneous	1/14	-	-
McBride [24]	2007	Case series	20	-/13.6±3.2	4/20 – Heterogeneous	4/20	-	-
Tomassoni [28]	1990	Case series	12	4.5-15/8.5±3.69	2/12 - Heterogeneous	2/8	-	4 (33.3%) no description of drop-outs
Total			639		201/639	112/379	76/205* 0/26§	

*Control group were subjects with congenital heart disease who did not exercise

§Control group were healthy subjects who performed the training program

#15 subjects same as Rhodes 2005

$ Same subjects utilised in Moalla 2006 and 2012 (32, 34)

^ No information regarding breakdown of number of Fontan subjects in group provided

Table 2 Description of rehabilitation program.

Reference	Setting	Exercise type	Program Duration (months)	Frequency (sessions/wk)	Duration (mins)	Intensity	Monitoring
Longmuir [30]#	Home	Fitness and motor skill development *	12	1	90-120	-	-
Brassard [41]	Hospital + Home	Aerobic + Resistance	2	3	20-30 + Resistance Training	Aerobic 50-80%HRpeak Resistance 12-15Rep Max	-
Cordina [36]	Supervised Gym	Resistance	5	3	60	80% of 1 Rep Max	Rate of Perceived Exertion
Minamisawa [31]	Home	Aerobic*	2-3	2-3	25-35	60-80% HRpeak	Manually taken HR 6 participants Holter electrocardiography
Opocher [40]	Hospital + Home	Aerobic*	2	2	30-45	HR at 50-70%VO2peak	HR monitor
McCall [25]	Hospital	Aerobic + Resistance	5	2-3	20-30	Aerobic HR at 50-70% VO2peak Resistance 12-15Rep max	-
Lichtman [22]	Hospital	Aerobic + Resistance	(36 sessions)	-	-	Borg RPE 12-13	Telemetry
Balfour [21]	Hospital	Aerobic* Education	3	3 + 2§	30-40	80-90%HRpeak ≥70%HRpeak Borg RPE	Manually taken HR
Dua [29]	Home	Aerobic*	2.5	5	5-10 if <3METs 10-30 if 3-5 METs 20-30 if >5METs	-	-
Fredriksen [37]	Supervised Gym	Aerobic + Education*	0.5 or 5	Daily or 2	-	65-80%HRpeak	HR monitor
Martinez-Quintana [23]	Hospital	Aerobic + Resistance	3	2	34 + Resistance Training	80%HRpeak Modified Borg (3-6)	-
Moalla 2006/2012 [32,34]	Home	Aerobic	3	3	60	Ventilatory anaerobic threshold±5beats/min	HR monitor
Moalla 2005 [33]	Home	Aerobic	3	3	60	Ventilatory threshold HR at 63.3±7.1% of VO2peak	HR monitor
Morrison [35]	Home	Exercise plan* + Motivational interviewing	6	-	-	-	-

Table 2. (continued)

Reference	Setting	Exercise type	Program Duration (months)	Frequency (sessions/wk)	Duration (mins)	Intensity	Monitoring
Rhodes 2005/2006 [19,26]	Hospital	Aerobic + Resistance	3	2 + 2[§]	60	Borg HR at Ventilatory anaerobic threshold	Manually taken HR
Ruttenberg [39]	Supervised Gym	Aerobic	2	3	5-30	65-75%HRpeak	Manually taken HR
Singh [27]	Hospital	Aerobic + Resistance	3	2 + 2[§]	60	Borg HR at Ventilatory anaerobic threshold	Manually taken HR
Muller [38]	Supervised Gym	Playful Exercise	3	1	60	-	-
McBride [24]	Hospital	Aerobic + Resistance	2-18 (Mean 6±4)	3	60	Aerobic Borg (12-15) HR at Ventilatory anaerobic threshold Resistance 60% of pre-training MVC	-
Tomassoni [28]	Hospital	Aerobic	3	2	60	60-80%HRpeak	Single lead electrocardiogram every 2-3 minutes

[#]Individually tailored
[*]Unmonitored voluntary training sessions at home in addition to hospital sessions
[§]Heart Rate
HR Metabolic Equivalent of Task
METS Maximum Voluntary contraction
MVC Individually tailored

Table 3 **Inclusion and exclusion criteria, Outcomes and Adverse Events.**

Reference	Inclusion criteria	Exclusion criteria	Tests to assess outcome	Results	Adverse events	Comments
Longmuir [30]	6-11y.o. ≥1 year post Fontan Participation approved by cardiologist	Disabilities that would limit participation	Serial CPET Activity Monitoring (accelerometer) Gross motor functional assessment Questionnaires Activity	Significant increase MVPA 35±31 min/week above baseline at 1 year Gross motor function 23±5 centiles Not Significant Motor skills not influenced by rehabilitation program Peak VO2 increased by 2.2±1.1ml/kg/min in both groups	Nil	Compliance ~50% Activity prescription vs Education
Brassard [41]	11-30y.o. Surgical procedure >2months before the study Sinus rhythm Blood SaO2 ≥90% Good candidates according to paediatric cardiologist (compliant, safety, geographical proximity, minimum height)	Characteristics which would exclude patient performing exercise program	Serial CPET Neuromuscular function - Ergoreflex Muscle Strength	Significant change Lower ergoreflex contribution to systolic blood pressure Not significant No change in Peak VO2 with exercise	Nil	
Cordina [36]	NYHA Class I-II Resting transcutaneous oxygen saturations >94% Geographical proximity Employment that would allow commitment to program	Frequent symptomatic arrhythmias Clinical evidence of heart failure Symptomatic inguinal hernia Severe aortic dilatation Functionally significant physical or intellectual impairment ≥2 regular exercise sessions per week	Serial CPET Muscle strength Body composition Cardiac MRI Muscle phosphorous spectroscopy Free breathing MR analysis (CPAP and Valsalva)	Significant increase Peak VO2 increased by 183±31ml/min (9.5±2.4%) Muscle strength 43±7% Muscle mass (1.9 in trainers vs -0.8 kg non-trainers) Oxygen pulse at rest and during exercise in trained vs detrained	TIA (3 days after most recent training session)	Attendance 76±5% Impaired phosphocreatinine recovery vs healthy controls Follow-up after 12 months detraining demonstrated significant fall in body lean mass

Table 3. (continued)

Reference	Inclusion criteria	Exclusion criteria	Tests to assess outcome	Results	Adverse events	Comments
Minamisawa [31]	>10y.o. Geographical proximity	Residual R-to-Left shunt increased during exercise Severe atrioventricular regurgitation Systemic ventricular dysfunction Exercise-induced dysrhythmias Symptomatic myocardial ischaemia	Serial CPET	Significant increase Peak VO2 increased from 23.7±5 to 26.4±5.4ml/kg/min (7%) Maximal workload (7%) Duration of exercise test 10.3±1.7 to 10.8±1.7min) Non-significant increase Oxygen pulse increased (p=0.073)	Nil	2 subjects excluded - did not complete training program
Opocher [40]	Born 1989-1996 Cavopulmonary Fontan	Characteristics which would exclude patient performing exercise program	Serial CPET	Significant increase Work Performed (11.3%) Peak VO2 ml/min (19%) Peak Oxygen pulse (19%) HR and oxygen pulse during submaximal exercise Non-significant increase Peak VO2 ml/kg/min (11%)	Nil	Compliance – 9 participants ≥90%, 1 participant <10%
McCall [25]	Not applicable	Not applicable	Serial CPET	After training Peak VO2 11.2ml/kg/min	Nil	Case study Participant listed for heart transplantation Baseline CPET stopped
Lichtman [22]	Not applicable	Not applicable	Serial CPET Body composition Questionnaire Short-Form 36 Health Survey (SF-36) Diet Depression scale	After training increased Exercise time (15.1%) Peak VO2 (25.6%) Quality of life (70.5%) by SF-36 Decreased depression scale score	Nil	Case study
Balfour [21]	Not described	Not described	Serial CPET	Significant increase Peak VO2 from 32±4 to 36±7ml/kg/min Duration of exercise test Significant decrease Resting systolic BP	Nil	Attendance 80% High drop-out and exclusion rate

Dua [29]	Not described	<16y.o. Pregnant Exercise contraindicated Cardiac surgery within 6 months Unable to walk on treadmill	Treadmill Exercise Test Questionnaires Physical activity Short-form 12 (SF12) Satisfaction with Life Scale Physical Self-Perception Profile-short clinical form (PSPPs) Activity monitoring Accelerometer Activity Diary	Significant increase Walking time Physical activity questionnaire Satisfaction with life Scale PSPPs Physical activity levels MVPA from 21.9±17.1 to 39.1±27	Nil	Peak VO2 not measured Worse NYHA class was associated with worse activity level
Fredriksen [37]	10-16 years old Geographical proximity Physical fitness equal or worse than peers	Characteristics which could influence test results Did not complete all tests	Serial CPET Questionnaires Youth Self report Child Behaviour check List Activity monitor	Significant increase Activity levels Exercise time Significant decrease Internalising behaviour Social problems Externalising behaviour	Nil	Control group had significantly higher peak VO2 vs. intervention group at baseline
Martinez-Quintana [23]	>14y.o. NYHA≥II-IV No change in pulmonary hypertension treatment for >6 months prior to entering study	Pulmonary hypertension treatment changed in follow-up period	6MWT Daily activity Pedometer Muscle strength Questionnaires Short-Form 12 Bloods (creatinine, haematocrit, amino-terminal pro-brain natriuretic peptide)	Improved NYHA class No change in 6MWT Daily activity Muscle strength Quality of life	Nil	Serial CPET not performed Peak VO2 not measured
Moalla 2006 [34]	12-15y.o. NYHAII or III Ventricle ejection fraction <40% Medical therapy stabilised for ≥3 months	Pacemaker Disabilities that would limit participation	Serial CPET Muscle Spectroscopy Pulmonary Function Tests	Significant increase Workload (45.2±8.0 vs. 58.5±7.4%) Peak VO2 (62.3±7.5 vs. 69.8±5.1%) Higher respiratory muscle oxygenation	Nil	Same subjects as per Moalla et al. 2012
Moalla 2012 [32]	12-15y.o. NYHAII or III Ventricle ejection fraction <40% Medical therapy stabilised ≥3 months	Pacemaker Disabilities that would limit participation	Serial CPET Muscle strength Muscle oxygenation	Significant increase Maximal voluntary contraction (101.6±14 vs. 120.±19.4Nm) Time to exhaustion (66.2±22.6 vs. 86±23)	Nil	Same subjects as Moalla et al. 2006

Table 3. (continued)

Reference	Inclusion criteria	Exclusion criteria	Tests to assess outcome	Results	Adverse events	Comments
Moalla 2005 [33]	12-16y.o. NYHAII-III Left ventricle ejection fraction <40% Medical therapy stabilised for ≥3 months	Pacemaker Disabilities that would limit participation	Serial CPET PFT 6MWT	Significant increase Ventilatory threshold increase of VO2 (18.3±1.1 vs. 23,8±1.0) 6MWT distance (13%) Non-significant increase Power output (106.9±5.4 vs. 115.6±7.1W) VO2mx (29.6±1.9 vs. 32.8±2.0 ml/min/kg)	Nil	
Morrison [35]	12-20 y.o.	Syndromic diagnosis Major learning difficulty Exercise contraindicated Left ventricular outflow tract obstruction Severe aortic stenosis	Serial CPET* Activity monitor Accelerometer Activity questionnaire	Significant increase Duration of exercise test (10.9±3.2 vs. 12.0±3.8minutes) Predicted peak VO2 (35.0±7.4 vs. 37.4±8.8ml/kg/min) MVPA (28.4±20.1 vs. 57.2±32.2) Non-significant increase METs (12.9±3.5 vs. 15.6±2.2)	Nil	
Rhodes (2005) [26]	8-17 y.o. Non-trivial congenital heart defect ≥1 surgical or interventional catheterisation procedure and/or significant residual haemodynamic effect Abnormal exercise function VO2 peak and/or Work rate peak <80% Commitment to attend and participate reliability in intervention	Exercise test abnormality Exercise induced arrhythmias, ST depression, hypertension, hypotension, cardiac chest pain, systemic desaturation<80% Conditions excluded Documented life-threatening arrhythmias not palliated by automatic internal cardiac defibrillator Moderate or severe dysfunction of either ventricle LVEF<40%	Serial CPET	Significant increase Peak VO2 (26.4±9.1 vs. 30.7±9.2ml/kg/min (16%)) Peak work rate (93±32 vs. 106±34W (14%)) Peak Oxygen pulse (7.6±2.8 vs. 9.7±4.1ml/beat (18%)) Peak exercise diastolic blood pressure (63±12 vs 71±8 mmHg (13%)) Similar improvement at ventilatory anaerobic threshold for above variables	Nil	

		Pulmonary artery hypertension >40 mmHg or requiring treatment with vasodilators Uncontrolled heart failure Acute inflammatory cardiac disease Significant coronary artery disease Resting oxygen saturation <90% Aortic stenosis; resting peak systolic gradient >50mmHg Pulmonary stenosis resting peak systolic gradient >50mmHg Severe systemic atrioventricular valve regurgitation Systemic hypertension (>95th percentile for age) Acute renal disease Acute hepatitis				
Rhodes 2006 [19]	Improved peak VO2 and/or peak work rate in Rhodes 2005 (26) ≥6/12 since last surgical or interventional catheterisation procedure	Exclusion of participant who did not improve VO2 peak and/or peak work rate in Rhodes 2005 (26)	Follow up CPET Questionnaires Child Health Questionnaire - Child Form-87 Physical activity Child Health Questionnaire - Parent Form 50	Significant increase Peak VO2 from baseline (11.2±12.1%) Predicted peak work rate (4.7±7.9%) Other findings Peak VO2 maintained post-rehabilitation >50% of participants (control and intervention) believed parents and doctors limited their activity	Nil	Follow-up 6.9±1.6 month after Rhodes et al. 2005
Ruttenberg [39]	Nature of Lesion ≥1 year since open heart surgery Geographical proximity	Not described	Serial CPET	Non-significant findings Peak VO2 (38.0ml/kg/min vs. 43.8ml/kg/min) Peak HR (158 vs. 185beats/min)	Nil	High drop-out (58%)

Table 3. (continued)

Reference	Inclusion criteria	Exclusion criteria	Tests to assess outcome	Results	Adverse events	Comments
Singh [27]	Referred for exercise testing at Children's Hospital ≥1 open-heart surgery or interventional catheterisation during infancy or early childhood Peak work rate and/or peak VO2 <80% predicted ≥6 months post last surgical or interventional catheterisation	Medical conditions and/or exercise test abnormalities that could pose health risk during exercise	Serial CPET HR recovery	Significant increase Peak VO2 (26.3±9.6 vs. 30.9±9.6) HR recovery at 1 and 3-minutes	Nil	Peak VO2 and 3-minute HR recovery improvements sustained 4-10 months after completion of intervention
Muller [38]	4-6 y.o. Congenital heart disease	Non-invasive brachio-ankle gradient > 20 mmHg (re-coarctation) Mean Doppler gradient across left or right ventricular outflow tract > 50 mmHg Mean Doppler gradient across an atrioventricular valve > 10 mmHg Severe valve regurgitation, or moderate valve regurgitation with ventricular dysfunction Right to left shunt (even if only present at exercise) Left to right shunt with dilatation or malfunction of an atrium or a ventricle Pulmonary hypertension (mean pulmonary arterial pressure > 25 mmHg) Heart failure needing drug therapy	Motor development test MOT4-6	Significant findings Subgroup with lower motor development improved 5% Non-significant findings Motor quotient increased (92 vs. 95)	Nil	CPET not performed

		Suspected or proven myocarditis or cardiomyopathy Arrythmia, pacemaker, or implanted defibrillator Suspected or known ion channel defects or other arrhythmogenic cardiomyopathies Marfan syndrome Syndromic diagnoses Physical handicaps that impede regular sport activities in the group				
McBride [24]	Awaiting heart transplantation Positive inotropic support	<6 years old Preexisting significant orthopedic or musculoskeletal abnormalities Significant cognitive delay that precluded formal exercise testing and training	Safety	1251/1508 training sessions conducted 615 hours dedicated to low-intensity aerobic exercise safely conducted	Two seizures	No CPET outcome measures Compliance 83%
Tomassoni [28]	Specific congenital cardiac abnormalities Geographical proximity Operative repair ≥13 months prior	Not described	Serial CPET	Significant increase Duration of exercise test (9.4 vs. 10.9minutes) Peak cardiac output (4.91 vs. 6.05L/min (23.4%)) Non-significant increase Cardiac index (4.82 vs. 5.71L/min p=0.055)	Nil	Did not measure VO2

*Submaximal test: Test stopped when participant reached 85% predicted HR for age. VO2 estimated with Bruce Cardiac Max equation
CPET Cardiopulmonary exercise test
y.o.: Years old
METs Metabolic equivalent
MVPA Moderate-to-Vigorous physical activity

Rehabilitation Program Outcomes

The studies employed numerous outcomes to assess the impact of their respective interventions. Their outcome measures and results are reported in detail in Table 3.

Exercise Capacity

Exercise capacity measured by peak oxygen consumption (peak VO2) was significantly increased in seven studies where this parameter was reported [21,26,27,31,34,36,40]. Morrison et al. demonstrated a significant increase in predicted peak VO2 [35]. There was a non-significant increase in peak VO2 in four studies [30,33,39,41] and no change in one study [37]. Five studies did not measure the effect of training on peak oxygen consumption [23,24,28,29,38]. Two studies illustrated that the increased exercise capacity could be maintained at six months [19] and four to 10 months [27] following rehabilitation.

Oxygen Pulse

Oxygen pulse is a surrogate measurement for stroke volume (the amount of oxygen consumed per heart beat, an index equal to stroke volume times oxygen extraction [42]). It was measured in four studies only [26,31,36,40]. Three studies reported a significant rise in oxygen pulse after completion of rehabilitation program [26,36,40] and Minimasawa et al. reported a non-significant increase [31].

Muscle strength

Four studies examined the effect of their interventions on muscle strength. Two studies established that muscle strength was significantly increased following training [32,36]. Brassard et al. demonstrated non-significant increase in muscle strength whilst Martinez-Quintana et al. found no change in strength following their respective interventions.

Activity Levels

Five studies reported on activity levels. Four reported statistically significant increase in activity levels [29,30,35,37] whilst Martinez-Quintana et al. reported no change in daily activity levels [23].

Quality of Life

The effect of cardiac rehabilitation on quality of life was investigated in four studies. Three studies reported improved quality of life [22,29,37] whilst Martinez-Quintana et al. reported no change in quality of life [23].

Adverse Effects

The adverse events that occurred in the reviewed literature are reported in Table 3. Notably, there were only three adverse events described in over 200 Fontan subjects who participated. Cordina et al. reported a transient ischaemic attack that took place three days following the latest training session. McBride et al. reported two seizures in participants with congenital heart defects receiving inotropic support whilst awaiting transplantation who may not have had a Fontan circulation. None of the adverse events reported were related to cardiac rehabilitation or exercise. In addition, no studies reported any cases of sudden cardiac death. Most clinical trials employed exclusion criteria that prevented subjects at increased risk, such as those with arrhythmias and ventricular dysfunction, from participating.

Discussion

One of the objectives of this review was to identify the safety of exercise rehabilitation in Fontan patients. The lack of adverse effects within Fontan participants convincingly demonstrates that cardiac rehabilitation is safe in this population, and further, the results indicate that they benefit from participation in these programs.

Unfortunately, few studies have investigated the physiological adaptations that occurred following cardiac rehabilitation with most focussing only on detecting improvements in exercise capacity. Longmuir et al. have evaluated neuromuscular function by assessing the ergoreflex and reported abnormal skeletal muscle function [41]. Cordina et al. have utilised muscle spectroscopy and cardiac MRI to determine physiological adaptations following rehabilitation. Limited application of these techniques has resulted in incomplete understanding of interactions between the centrally mediated cardiovascular factors and the peripherally mediated factors that contribute to exercise intolerance. It is therefore very difficult to ascertain the best intervention for augmenting exercise capacity in Fontan circulation. However, it is well-established the Fontan patients' cardiac output is subnormal and failure to increase stroke volume is a significant contributory factor [26].

The four studies that measured oxygen pulse employed different rehabilitation regimens [26,31,36,40]. Cordina et al. is most notable as it demonstrated that specific resistance training of lower limb muscles increased muscle mass and subsequently enhanced the muscle pump. The muscle pump increased systemic venous return and hence preload causing significant improvement in stroke volume, cardiac output and exercise capacity. This seminal finding indicates that resistance training must be incorporated into future cardiac rehabilitation programs for Fontan circulation subjects. The other studies utilised aerobic only [31,40] or aerobic and resistance training [26] demonstrating that aerobic training is still an important component in a cardiac rehabilitation program.

In order for exercise capacity to be enhanced, rehabilitation needs to be above a sufficient threshold and within the individual's training-sensitive zone [43]. Training in this zone can be achieved by using different combinations of exercise intensity, duration and frequency. This becomes particularly complicated when designing cardiac rehabilitation programs for children who require age appropriate interventions to maximise motivation. As a result there was considerable methodological variation in these factors between studies (Table 2). Intensity was set at a percentage of peak heart rate, peak oxygen consumption or rate or perceived exertion or ventilatory anaerobic threshold. Importantly, methods of monitoring

intensity were either not described or were inadequate in many studies [21,23–27,29–31,39,41]. The duration of programs also varied with time periods between two weeks [37] to 18 months [24] and a median duration of three months employed. The training frequency also varied and ranged from one training session per week [30,38] to a daily training session [37] with a median frequency of three per week. Several studies incorporated two voluntary sessions in addition to those supervised, but compliance with voluntary sessions was not measured [19,21,26,27]. The disparity in program characteristics prevents optimal duration, frequency or intensity of a rehabilitation program from being established.

Active lifestyles are an essential component of maintaining a healthy lifestyle in children and adults [44]. An active lifestyle positively impacts on cardiovascular health. The exercise intolerance in Fontan circulation subjects is further compounded by physical inactivity [18]. McCrindle et al. have reported that physical inactivity is independent to an individual's exercise capacity. However, several studies, one investigating Fontan participants exclusively, have reported statistically significant and clinically meaningful increased activity levels following cardiac rehabilitation [29,30,35,37].

One of the goals of a cardiac rehabilitation program should be the enhancement of quality of life of the child or adolescent. Disappointingly, only one case study has investigated the impact of training on quality of life in a Fontan participant [22]. Lichtman et al. reported that rehabilitation resulted in improved quality of life and decreased depression. Three clinical trials, that included Fontan participants, have evaluated the impact on quality of life in the wider congenital heart defect population. Dua et al. reported improved satisfaction with life and self-esteem following exercise-training period [29]. Fredrikson et al. reported reduced internalising behaviour such as withdrawal and somatic complaints after rehabilitation. However, they also reported a significant reduction in total problems in the control group only. Furthermore, Martinez-Quintana et al. reported no improvement in quality of life following their intervention in pulmonary hypertension subjects. These studies were limited by small sample size and the evidence regarding impact of rehabilitation on quality of life is unclear. Future cardiac rehabilitation in Fontan subjects should ascertain what impact the intervention has on participants' quality of life and self-esteem.

Conclusion

The results in the over 200 Fontan participants in the literature convincingly demonstrates that cardiac rehabilitation is safe in this population and further, they deeply benefit from participation in an exercise program with improved exercise tolerance, muscle strength, activity levels and quality of life. Long-term sustainability in these areas still needs to be confirmed.

Therefore, we believe that a cardiac rehabilitation program should become standard of care within this population. The program must incorporate lower limb resistance training to augment the muscle pump and aerobic exercise. Programs should be at least two months with at least twice weekly training sessions, however disparate programs in the literature prevents the development of guidelines regarding optimal characteristics. Future research should also seek to understand the physiological adaptations that occur following completion of cardiac rehabilitation and also measure impact on activity levels and quality of life.

Disclosures

Yves d'Udekem is a NHMRC Clinician Practitioner Fellow (1082186). The Victorian Government's Operational Infrastructure Support Program supported this research project.

Financial Assistance

None declared

Acknowledgements

The authors thank our research assistants, Dr Aneta Kotevski, Ms Janina Chapman, Ms Ingrid King, Ms Charlotte Verrall, Ms Megan Upjohn and Ms Lisa Cowcher for their invaluable assistance in the creation and maintenance of the Registry and to Belinda Bortone for administrative support. The authors acknowledge support provided to the Murdoch Childrens Research Institute by the Victorian Government's Operational Infrastructure Support Program.

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