Exercise training in children and young adults with congenital heart disease

rationale, effects and impact on quality of life

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Exercise Training In Children And Young Adults With Congenital Heart Disease: Rationale, Effects And Impact On Quality Of Life

Inspanningstraining in kinderen en jong volwassenen met een aangeboren hartafwijking: rationale, effect en impact op kwaliteit van leven

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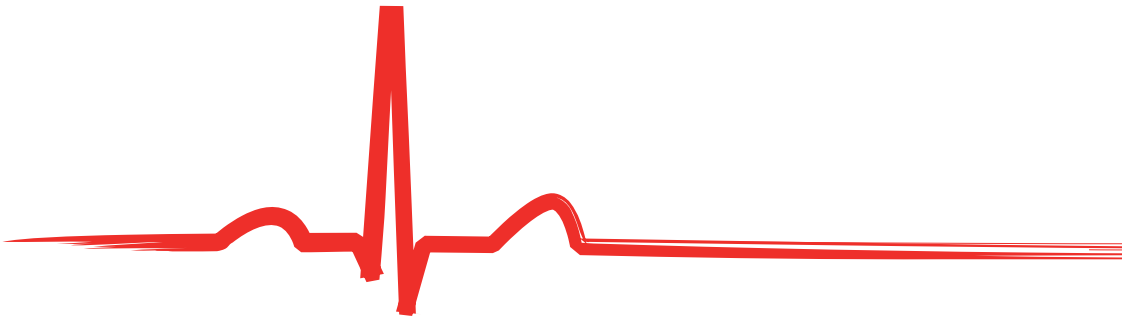
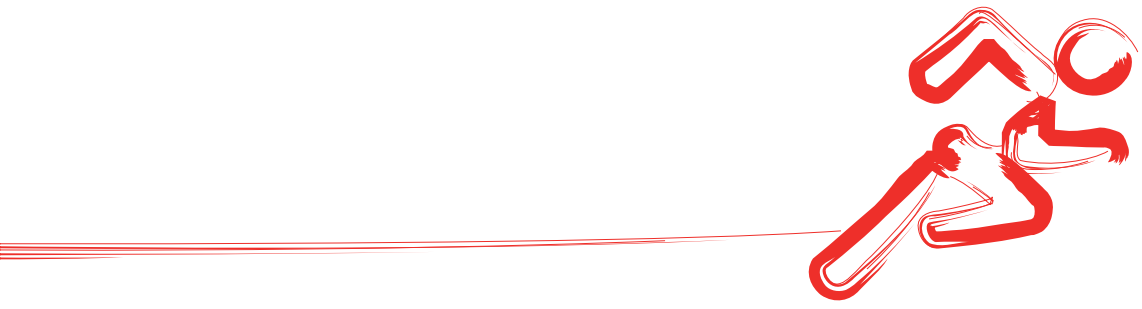
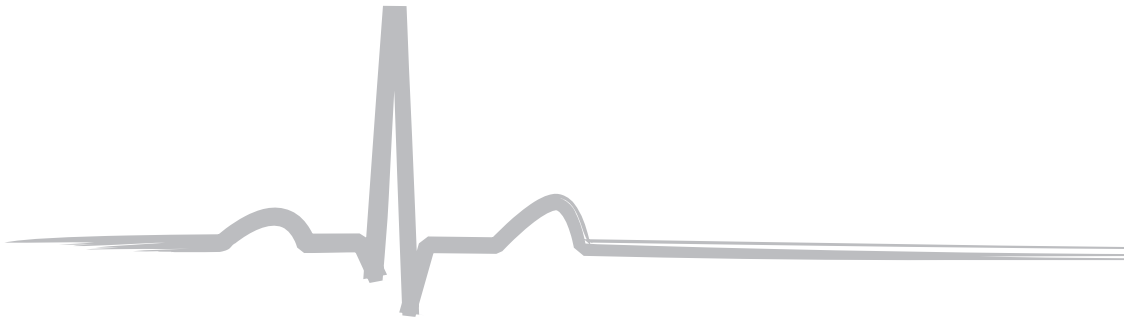


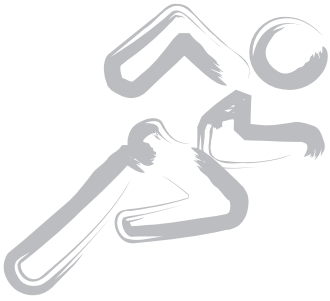
Part 1





Chapter 1

General introduction.



OUTLINE GENERAL INTRODUCTION

In this chapter an overview is given on congenital heart disease (ConHD), with the focus on tetralogy of Fallot (ToF) and Fontan circulation. Guidelines for exercise training programs will shortly be discussed. Finally, the aims and outline of this thesis will be presented.

CONGENITAL HEART DISEASE

In a recent review the prevalence of ConHD in Europe was estimated to be around 8.2 per 1000 live births[1]. As a result of improved techniques for diagnosis and treatment, survival of patients with ConHD into adulthood is increasing. As a result of improved survival, the scope of research in ConHD has shifted from means to reduce mortality to prevention of morbidity and improving quality of life[2]. Research in the area of morbidity reduction includes, among many other subjects, enhancing exercise capacity. Decreased exercise capacity may limit participation in work, social events and other common daily activities[3].

ConHD patients can be categorized based on severity of their ConHD. Severe ConHD may be associated with cyanosis and generally requires surgical intervention early in life. Frequently, residual loading abnormalities persist, even after optimal surgical treatment. Patients with ToF and with univentricular heart are among those with the most severe ConHD diagnoses[4]. This thesis therefore focusses on those two subgroups within the ConHD population.

TETRALOGY OF FALLOT

Tetralogy of Fallot (ToF) is the most common diagnosis (3.5-5%) within the group of ConHD that present with cyanosis. The prevalence is about 0.34 per 1000 live births[1, 5]. The diagnosis ToF consists of 4 features: 1) ventricular septal defect (VSD), 2) right ventricular outflow obstruction, 3) over-riding of the aorta and 4) right ventricular hypertrophy (figure 1)[5]. Surgical intervention aims to close of the VSD, create an unobstructed right ventricular outflow tract and create a competent pulmonary valve[5]. However, residual hemodynamic alterations, such as pulmonary regurgitation, will remain present inevitably[5]. Surgical intervention has decreased early mortality and enhanced life expectancy, but residual pulmonary regurgitation may cause right ventricle volume overload. This will result in dilatation of the right ventricle. As a result the QRS complex widens, which among other factors, such as scars from open heart surgery, has been related to an increased risk of ventricular arrhythmias. The residual hemodynamic alterations may lead to loss of exercise capacity, morbidity and mortality during the second and third decades of life[6, 7].

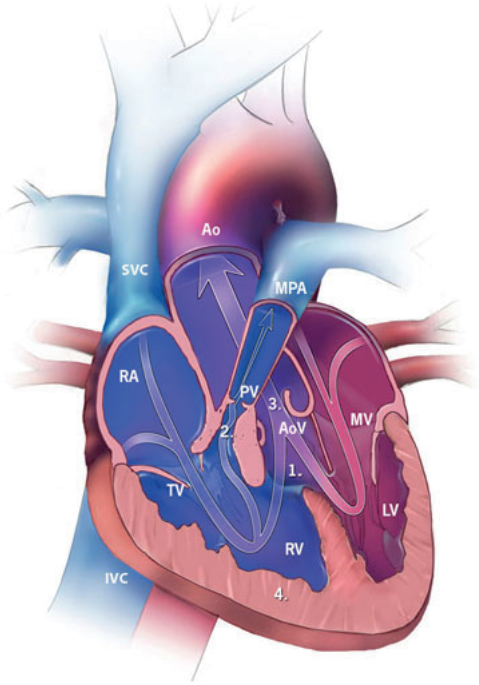


Figure 1: Tetralogy of Fallot
RA: right atrium, RV: right ventricle, LA: left atrium, LV: left ventricle, SVC superior vena cava, IVC: inferior vena cava, MPA: main pulmonary artery, Ao: aorta, TV: tricuspid valve, PV: pulmonary valve. AoV: aorta valve. Image provided by Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities.

UNIVENTRICULAR HEART, THE FONTAN CIRCULATION

The term univentricular heart embodies a variety of ConHD diagnoses with different underlying anatomy[8]. The common feature that combines them is the lack of two well-developed ventricles[8]. The most commonly known type of univentricular heart is the hypoplastic left heart syndrome, with a prevalence of 2.3 cases per 10 000 live births (figure 2)[8]. Surgical management of the univentricular heart is palliative and aims to provide unobstructed systemic outflow, systemic as well as pulmonary venous return and pulmonary blood flow[8]. Depending on the underlying pathology a series of operations are performed. The pulmonary circulation is separated from the systemic circulation. Both the inferior and superior vena cava are connected to the pulmonary artery resulting in a total cavopulmonary connection (TCPC)[8]. The TCPC can be obtained with either an extracardiac conduit (ECC) or an intracardial lateral tunnel (ILT) (figure 3).

The Fontan circulation allows patients to reach adulthood and have a good quality of live[9]. Nevertheless, sequelae persist in patients with a Fontan circulation. Unfavorable

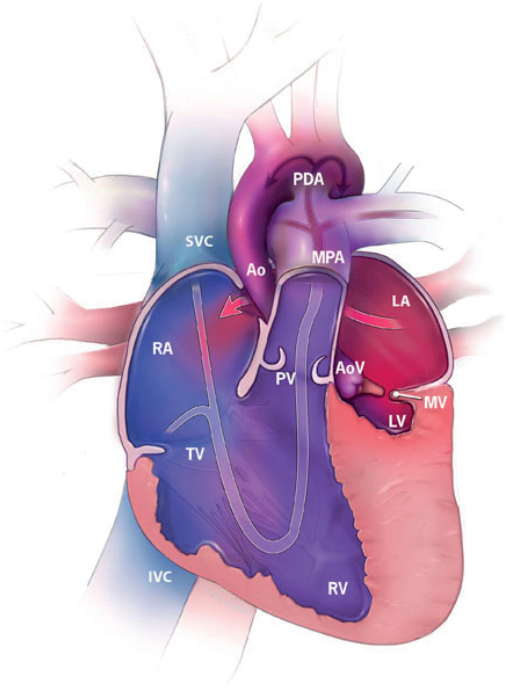


Figure 2: Hypoplastic left heart syndrome
RA: right atrium, RV: right ventricle, LA: left atrium, LV: left ventricle, SVC superior vena cava, IVC: inferior vena cava, MPA: main pulmonary artery, Ao: aorta, PDA: patent ductus arteriosis, TV: tricuspid valve, MV: mitral valve. PV: pulmonary valve, AoV: aorta valve. Image provided by Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities.

hemodynamics can lead to a failing Fontan circulation, with poorer exercise tolerance, lower cardiac output, arrhythmia, and early mortality[9].

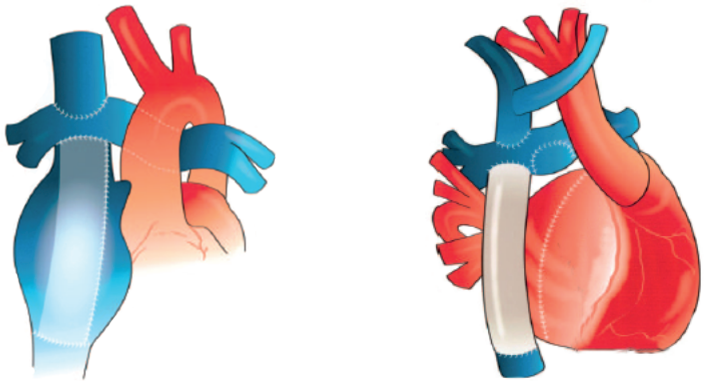


Figure 3: Intra lateral tunnel and extra cardiac conduit
Adapted from Khairy et al[8].

EXERCISE CAPACITY IN CONHD PATIENTS

Exercise capacity is the ability to be physically active. Physical activity is defined as any active bodily movements that increase metabolic rate above the resting level[10]. This is determined by the cardiopulmonary system. This system has to provide the body with enough blood flow to sufficiently support the metabolic needs associated with physical activity[11]. During activity the heart rate, contractility of the ventricles and preload increases and vascular resistance decreases in healthy persons. In contrast, ConHD patients may be limited in those factors, due to an inability to increase heart rate due to chronotropic incompetence, ventricular dysfunction and changes in pulmonary vasculature. This can result in limited capacity to increase cardiac output, and thus a limitation in physical activity[11]. Adult patients with a ConHD have a diminished physical active ability compared to healthy peers. Within the ConHD group the physical activity ability diminishes with the increase of severity of the ConHD diagnosis[3]. Patients with a univentricular heart have, on average, a lower exercise capacity than patients with a corrected tetralogy of Fallot[3].

GUIDELINES FOR PHYSICAL ACTIVITY AND EXERCISE TRAINING PROGRAM

Current public health guidelines for children, as well as children with congenital heart disease, suggest at least 60 minutes of moderate-to-vigorous physical activity daily[10]. A lack of physical activity can result in suboptimal physical, emotional and psychosocial development[10, 12]. Adolescents with ConHD are not as physically active as their healthy peers[13]. If a person is less active as an adolescent he or she is very likely to be less active as an adult[14]. Overall, adults with ConHD have a lower exercise capacity, which may limit participation in work, social events and other common daily activities as well as increase their risk for mortality[3, 7].

The lack of physical activity in patients with a ConHD may be the result of overprotection from parent, teachers and peers and the lack of knowledge if physical activity is allowed[15-17].

Exercise training in patients with acquired heart disease has been studied lengthily in well-designed trials. Exercise capacity in those patients increased after training program as well as improvement of cardiac function without adverse remodeling of the heart[18]. Even more, mortality and morbidity in this population was reduced after a training program[19].

In contrast to the numerous studies performed in patients with acquired heart disease, only a few studies have investigated exercise training in patients with congenital heart diseases. Some studies have been performed to evaluate the effect of exercise training

on exercise capacity in this patient population[20-50]. Some of the studies lack a control group, or a well-structured training design. None of the studies investigated the effect that exercise training has on the heart.

THE AIM AND OUTLINE OF THE TOFFIT TRIAL

The aim of the trial presented in this thesis was to assess whether exercise training in children and young adults with corrected tetralogy of Fallot as well as Fontan circulation would result in changes in physical fitness, cardiac remodeling and quality of life.

Design

A multi-center prospective, randomized controlled trial was conducted in 5 tertiary referral centers for ConHD in the Netherlands (Academic Medical Centre in Amsterdam, Leiden University Medical Centre in Leiden, Erasmus MC-Sophia in Rotterdam, Radboud University Nijmegen Medical Centre in Nijmegen and University Medical Centre Utrecht-Wilhelmina Children's Hospital in Utrecht). The study was designed according to Consolidated Standards of Reporting Trials (CONSORT) guidelines[51].

Participants

Adolescents between the age of 10 to 25 years with either corrected tetralogy of Fallot or Fontan circulation were eligible. Surgical correction of tetralogy of Fallot had to be performed through a transatrial-transpulmonary approach. The Fontan circulation had to be a modern total cavopulmonary connection (TCPC), either an extracardial conduit (ECC) or an intracardial lateral tunnel (ILT).

Patients with ventricular outflow tract obstruction greater than 60 mmHg were excluded, as were all patients who were mentally unable to follow a training program.

Patients were identified through the local databases of the participating hospitals and if they participated a signed written informed consent was obtained. The study complied with the Declaration of Helsinki. Institutional Ethics Committees of all participating centers approved the research protocol.

Intervention

Randomization of participants was performed by an independent blinded researcher on a 2:1 ratio to either the exercise or control-group. Stratification was based on gender, congenital heart defect, and age group (10- 12 years, 13-14 years, 15-17 years, 18-25 years).

The exercise-group was enrolled in a 12 week standardized aerobic dynamic exercise training program with three 1-hour sessions per week. The training hour, supervised by a local physiotherapist, was divided in 40 minutes of aerobic dynamic training, and 10

minutes of both warming up and cooling down. Participants were given a heart rate monitor (SR400, Polar Electro BV, the Netherlands) to help them perform their exercises within the predetermined heart rate range. This range was set at 60 to 70 percent of the heart rate reserve, which was determined by cardiopulmonary exercise test prior to the training program.

All physiotherapists were instructed prior to the start of the program to ensure that standardized implementation of the program occurred. The control-group was instructed to continue their normal daily life.

Cardio-pulmonary fitness

The capacity of the cardiopulmonary system to provide the body with enough blood flow to sufficiently support the metabolic needs if maximal stressed is assessed by cardio-pulmonary exercise testing[11]. During cardiopulmonary exercise testing ECG monitoring registers heart rate, rhythm disturbances and ischemic changes in the myocardium[11]. Gas analysis registers oxygen uptake (VO_2), carbon dioxide outflow (VCO_2) and minute ventilation (VE). PeakVO_2 is the primary indicator of physical capacity, and is measured at maximal exercise capacity[11]. PeakVO_2 varies with body mass. Therefore peakVO_2 is indexed by weight[11].

Children do not always reach the peak of their physical capacity[52]. If maximal exercise capacity is not reached an indicator of physical fitness can be calculated during submaximal exercise. One of these indices is the minute ventilation to carbon dioxide production slope. The minute ventilation rises linearly with the carbon dioxide production until the ventilatory anaerobic threshold is reached. The slope is an index of gas exchange efficiency during exercise. An elevated slope indicates that more liters of air are needed to eliminate the carbon dioxide. It is associated with ventilation perfusion mismatch[11].

Daily physical activity

Daily physical activity can be measured objectively as well as subjectively[53]. Self-reports tend to overestimate both the quantity as well as the intensity of the reported activity[53]. Therefore an objective monitoring tool is preferable[53]. Doubly labeled water is the gold standard to assess physical activity. However, this is an invasive and expensive procedure. Therefore this is not suitable for daily practice[53]. The most used and reliable alternative to measure physical activity is an accelerometer[53]. An accelerometer counts the acceleration per user specified time interval. The counts recorded by the meter are translated to a physical activity level (e.g. sedentary, light, moderate, vigorous) by applying cut-off points. Cut-off values differ per age-group. A lack of agreement consists on the value of the cut-off points[54]. In a recent review the cut-off values established by Freedson at al. were shown to be most accurate in predicting physical activity level[54].

Imaging the heart: magnetic resonance imaging and echocardiography

Magnetic resonance imaging (MRI) allows unrestricted access to the cardiovascular anatomy and physiology. This allows quantification of volumes of chambers as well as of flow velocities of vessels regardless of their geometry and position within the body[55]. In addition, MRI does not require ionizing radiation[55]. As the body matures, the body size, including the volumes of the chambers of the heart, increase. To adjust for the impact of increasing size volume is indexed for body mass area (BSA)[56]. End-diastolic volume, end-systolic volume and stroke volumes (all indexed for BSA) are commonly used parameters of cardiac size and global function.

During exercise abnormal responses of the heart may be provoked[57]. Several alternatives, besides exercises whilst the patient is in an MRI-scanner, can be used to stress the heart during imaging. To assess ventricular function during stress low-dobutamine infusion is a practical tool that can safely be used, even in children[58, 59].

In contrast to the MRI, echocardiography, although limited by an acoustic window, is easily available and low in cost. Echocardiography allows comprehensive and reproducible information on both global as well as regional ventricular function and dimensions of the heart[60].

Electrocardiography

ECG and 24-hour ECG (Holter) give insight in the rhythm and conduction times in patients with ConHD. Arrhythmias are commonly present in patients post cardiac operation and have been associated with worse clinical outcome[61].

Assessment of neurohormonal status

Increased N-terminal fragment brain natriuretic peptide (NT-pro-BNP) has been associated with impaired cardiac function in congenital heart disease[62]. NT pro-BNP is increased in patients with acquired heart disease and heart failure[63]. Exercise training programs have resulted in significant decrease of NT pro-BNP in patients with heart failure[63].

Other neurohormonal markers that indicate adrenergic and RAAS activation have been associated with heart failure in congenital heart disease patients[64]. Whether exercise training decreases those markers is not yet known in patients with ConHD.

THE STRUCTURE OF THIS THESIS

In **this chapter (1)** a general introduction is given. In **chapter 2** an overview is given of exercise program studies in ConHD patients. In **chapter 3** the long-term outcomes of transatrial-transpulmonary repair of tetralogy of Fallot are discussed. The findings in

that chapter and extensive datasets available in literature provided the rationale for the studies described in the subsequent chapters. In **chapters 4 up to 9** the main findings of TOFFIT randomized controlled trial are discussed. **Chapter 4** focuses on the change in physical fitness as well as the change in daily physical activity in response to an exercise training program. **Chapter 5** describes cardiac remodeling after an exercise training program. **Chapter 6** focuses on the changes in regional ventricular performance. **Chapter 7** evaluates changes in wall shear stress in the pulmonary artery of Fontan patients after an exercise training program. In **chapter 8** the influences of an exercise training program on quality of live is discussed. In **chapter 9** the moderating effect of parental mental health on the efficacy of exercise training on health-related quality of life in adolescents is discussed. **Chapter 10** summarizes the main findings of the study and provides future perspectives. In **chapter 11** a summary is given and in **chapter 12** a Dutch summary is given.

REFERENCES

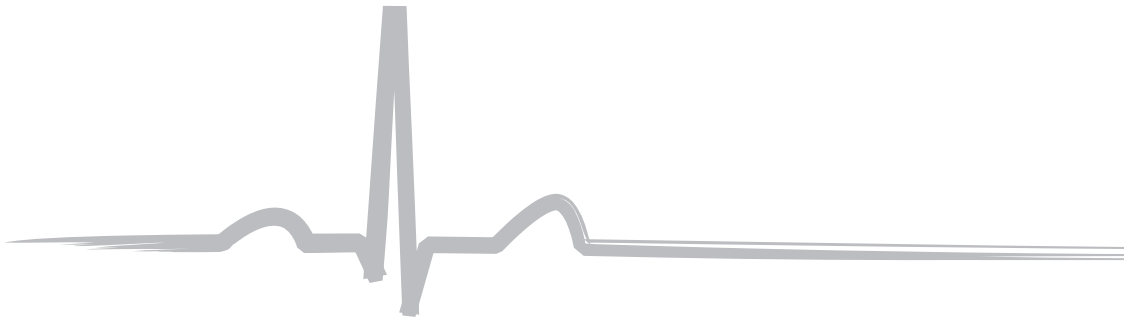
1. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: A systematic review and meta-analysis. *J Am Coll Cardiol*. 2011;58:2241-2247
2. Opotowsky AR, Siddiqi OK, Webb GD. Trends in hospitalizations for adults with congenital heart disease in the u.S. *J Am Coll Cardiol*. 2009;54:460-467
3. Kempny A, Dimopoulos K, Uebing A, Moceri P, Swan L, Gatzoulis MA, Diller GP. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life--single centre experience and review of published data. *Eur Heart J*. 2012;33:1386-1396
4. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: Changing prevalence and age distribution. *Circulation*. 2007;115:163-172
5. Apitz C, Webb GD, Redington AN. Tetralogy of fallot. *Lancet*. 2009;374:1462-1471
6. Orwat S, Diller GP. Risk stratification in adults with repaired tetralogy of fallot: The long journey from clinical parameters and surface ecg to in-depth assessment of myocardial mechanics, volume and pressure loading. *Heart*. 2014;100:185-187
7. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: Comparative severity, correlates, and prognostic implication. *Circulation*. 2005;112:828-835
8. Khairy P, Poirier N, Mercier LA. Univentricular heart. *Circulation*. 2007;115:800-812
9. Gewillig M. The fontan circulation. *Heart*. 2005;91:839-846
10. Takken T, Giardini A, Reybrouck T, Gewillig M, Hovels-Gurich HH, Longmuir PE, McCrindle BW, Paridon SM, Hager A. Recommendations for physical activity, recreation sport, and exercise training in paediatric patients with congenital heart disease: A report from the exercise, basic & translational research section of the european association of cardiovascular prevention and rehabilitation, the european congenital heart and lung exercise group, and the association for european paediatric cardiology. *Eur J Prev Cardiol*. 2012;19:1034-1065
11. Rhodes J, Ubeda Tikkanen A, Jenkins KJ. Exercise testing and training in children with congenital heart disease. *Circulation*. 2010;122:1957-1967
12. Moola F, Fusco C, Kirsh JA. The perceptions of caregivers toward physical activity and health in youth with congenital heart disease. *Qual Health Res*. 2011;21:278-291
13. Lunt D, Briffa T, Briffa NK, Ramsay J. Physical activity levels of adolescents with congenital heart disease. *Aust J Physiother*. 2003;49:43-50
14. Telama R, Yang X, Viikari J, Valimaki I, Wanne O, Raitakari O. Physical activity from childhood to adulthood: A 21-year tracking study. *Am J Prev Med*. 2005;28:267-273
15. Reybrouck T, Mertens L. Physical performance and physical activity in grown-up congenital heart disease. *Eur J Cardiovasc Prev Rehabil*. 2005;12:498-502
16. Longmuir PE, McCrindle BW. Physical activity restrictions for children after the fontan operation: Disagreement between parent, cardiologist, and medical record reports. *Am Heart J*. 2009;157:853-859
17. Dua JS, Cooper AR, Fox KR, Graham Stuart A. Physical activity levels in adults with congenital heart disease. *Eur J Cardiovasc Prev Rehabil*. 2007;14:287-293
18. Sandri M, Kozarez I, Adams V, Mangner N, Hollriegel R, Erbs S, Linke A, Mobius-Winkler S, Thiery J, Kratzsch J, Teupser D, Mende M, Hambrecht R, Schuler G, Gielen S. Age-related effects of exercise training on diastolic function in heart failure with reduced ejection fraction: The leipzig exercise

intervention in chronic heart failure and aging (leica) diastolic dysfunction study. *Eur Heart J*. 2012; 33:1758-1768

19. Swank AM, Horton J, Fleg JL, Fonarow GC, Keteyian S, Goldberg L, Wolfel G, Handberg EM, Bensimhon D, Illiou MC, Vest M, Ewald G, Blackburn G, Leifer E, Cooper L, Kraus WE. Modest increase in peak vo2 is related to better clinical outcomes in chronic heart failure patients: Results from heart failure and a controlled trial to investigate outcomes of exercise training. *Circ Heart Fail*. 2012;5: 579-585
20. Cordina RL, O'Meagher S, Karmali A, Rae CL, Liess C, Kemp GJ, Puranik R, Singh N, Celermajer DS. Resistance training improves cardiac output, exercise capacity and tolerance to positive airway pressure in fontan physiology. *Int J Cardiol*. 2013;168:780-788
21. Winter MM, van der Bom T, de Vries LC, Balducci A, Bouma BJ, Pieper PG, van Dijk AP, van der Plas MN, Picchio FM, Mulder BJ. Exercise training improves exercise capacity in adult patients with a systemic right ventricle: A randomized clinical trial. *Eur Heart J*. 2012;33:1378-1385
22. Muller J, Pringsheim M, Engelhardt A, Meixner J, Halle M, Oberhoffer R, Hess J, Hager A. Motor training of sixty minutes once per week improves motor ability in children with congenital heart disease and retarded motor development: A pilot study. *Cardiol Young*. 2012:1-5
23. Moalla W, Elloumi M, Chamari K, Dupont G, Maingourd Y, Tabka Z, Ahmaidi S. Training effects on peripheral muscle oxygenation and performance in children with congenital heart diseases. *Appl Physiol Nutr Metab*. 2012;37:621-630
24. Martinez-Quintana E, Miranda-Calderin G, Ugarte-Lopetegui A, Rodriguez-Gonzalez F. Rehabilitation program in adult congenital heart disease patients with pulmonary hypertension. *Congenit Heart Dis*. 2010;5:44-50
25. Dua JS, Cooper AR, Fox KR, Graham Stuart A. Exercise training in adults with congenital heart disease: Feasibility and benefits. *Int J Cardiol*. 2010;138:196-205
26. Lichtman SW, Caravano M, Schneyman M, Howell B, King ML. Successful outpatient cardiac rehabilitation in an adult patient post-surgical repair for tricuspid valve atresia and hypoplastic right ventricle: A case study. *J Cardiopulm Rehabil Prev*. 2008;28:48-51
27. Amiard V, Jullien H, Nassif D, Bach V, Maingourd Y, Ahmaidi S. Effects of home-based training at dyspnea threshold in children surgically repaired for congenital heart disease. *Congenit Heart Dis*. 2008;3:191-199
28. Singh TP, Curran TJ, Rhodes J. Cardiac rehabilitation improves heart rate recovery following peak exercise in children with repaired congenital heart disease. *Pediatr Cardiol*. 2007;28:276-279
29. McBride MG, Binder TJ, Paridon SM. Safety and feasibility of inpatient exercise training in pediatric heart failure: A preliminary report. *J Cardiopulm Rehabil Prev*. 2007;27:219-222
30. Rhodes J, Curran TJ, Camil L, Rabideau N, Fulton DR, Gauthier NS, Gauvreau K, Jenkins KJ. Sustained effects of cardiac rehabilitation in children with serious congenital heart disease. *Pediatrics*. 2006; 118:e586-593
31. Moalla W, Maingourd Y, Gauthier R, Cahalin LP, Tabka Z, Ahmaidi S. Effect of exercise training on respiratory muscle oxygenation in children with congenital heart disease. *Eur J Cardiovasc Prev Rehabil*. 2006;13:604-611
32. Brassard P, Poirier P, Martin J, Noel M, Nadreau E, Houde C, Cloutier A, Perron J, Jobin J. Impact of exercise training on muscle function and ergoreflex in fontan patients: A pilot study. *Int J Cardiol*. 2006;107:85-94
33. Rhodes J, Curran TJ, Camil L, Rabideau N, Fulton DR, Gauthier NS, Gauvreau K, Jenkins KJ. Impact of cardiac rehabilitation on the exercise function of children with serious congenital heart disease. *Pediatrics*. 2005;116:1339-1345

34. Opocher F, Varnier M, Sanders SP, Tosoni A, Zaccaria M, Stellin G, Milanesi O. Effects of aerobic exercise training in children after the fontan operation. *Am J Cardiol*. 2005;95:150-152
35. Moalla W, Gauthier R, Maingourd Y, Ahmaidi S. Six-minute walking test to assess exercise tolerance and cardiorespiratory responses during training program in children with congenital heart disease. *Int J Sports Med*. 2005;26:756-762
36. Therrien J, Fredriksen P, Walker M, Granton J, Reid GJ, Webb G. A pilot study of exercise training in adult patients with repaired tetralogy of fallot. *Can J Cardiol*. 2003;19:685-689
37. Minamisawa S, Nakazawa M, Momma K, Imai Y, Satomi G. Effect of aerobic training on exercise performance in patients after the fontan operation. *Am J Cardiol*. 2001;88:695-698
38. Fredriksen PM, Kahrs N, Blaasvaer S, Sigurdsen E, Gundersen O, Roeksund O, Norgaand G, Vik JT, Soerbye O, Ingjer E, Thaulow E. Effect of physical training in children and adolescents with congenital heart disease. *Cardiol Young*. 2000;10:107-114
39. Sklansky MS, Pivarnik JM, O'Brian Smith E, Morris J, Bricker JT. Exercise training hemodynamics and the prevalence of arrhythmia's in children following tetralogy of fallot repair. *Pediatric Exercise Science*. 1994;6:188-200
40. Balfour IC, Drimmer AM, Nouri S, Pennington DG, Hemkens CL, Harvey LL. Pediatric cardiac rehabilitation. *Am J Dis Child*. 1991;145:627-630
41. Tomassoni TL, Galioto FM, Jr., Vaccaro P, Vaccaro J. Effect of exercise training on exercise tolerance and cardiac output in children after repair of congenital heart disease. *Sports Training, Med and Rehab*. 1990;2:57-62
42. Peja M, Boros A, Toth A. [effect of physical training on children after reconstructive heart surgery]. *Orv Hetil*. 1990;131:2085-2086, 2089-2090
43. Longmuir PE, Tremblay MS, Goode RC. Postoperative exercise training develops normal levels of physical activity in a group of children following cardiac surgery. *Pediatr Cardiol*. 1990;11:126-130
44. Calzolari A, Turchetta A, Biondi G, Drago F, De Ranieri C, Gagliardi G, Giambini I, Giannico S, Kofler AM, Perrotta F, et al. Rehabilitation of children after total correction of tetralogy of fallot. *Int J Cardiol*. 1990;28:151-158
45. Vaccaro P, Galioto FM, Jr., Bradley LM, Vaccaro J. Effect of physical training on exercise tolerance of children following surgical repair of d-transposition of the great arteries. *J Sports Med Phys Fitness*. 1987;27:443-448
46. Longmuir PE, Turner JA, Rowe RD, Olley PM. Postoperative exercise rehabilitation benefits children with congenital heart disease. *Clin Invest Med*. 1985;8:232-238
47. Bradley LM, Galioto FM, Jr., Vaccaro P, Hansen DA, Vaccaro J. Effect of intense aerobic training on exercise performance in children after surgical repair of tetralogy of fallot or complete transposition of the great arteries. *Am J Cardiol*. 1985;56:816-818
48. Ruttenberg HD, Adams TD, Orsmond GS, Conlee RK, Fisher AG. Effects of exercise training on aerobic fitness in children after open heart surgery. *Pediatr Cardiol*. 1983;4:19-24
49. Mathews RA, Nixon PA, Stephenson RJ, Robertson RJ, Donovan EF, Dean F, Fricker FJ, Beerman LB, Fischer DR. An exercise program for pediatric patients with congenital heart disease: Organizational and physiologic aspects. *J Cardiac Rehabil*. 1983;3:467-475
50. Goldberg B, Fripp RR, Lister G, Loke J, Nicholas JA, Talner NS. Effect of physical training on exercise performance of children following surgical repair of congenital heart disease. *Pediatrics*. 1981;68: 691-699
51. Schulz KF, Altman DG, Moher D, Group C. Consort 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332

52. Armstrong N, van Mechelen W. Aerobic fitness. *Paediatric exercise science and medicine*. Oxford: Oxford University Press; 2008:97-108.
53. Longmuir PE, Brothers JA, de Ferranti SD, Hayman LL, Van Hare GF, Matherne GP, Davis CK, Joy EA, McCrindle BW, on behalf of the American Heart Association Atherosclerosis H, Obesity in Youth Committee of the Council on Cardiovascular Disease in the Y. Promotion of physical activity for children and adults with congenital heart disease: A scientific statement from the american heart association. *Circulation*. 2013;127:2147-2159.
54. Kim Y, Beets MW, Welk GJ. Everything you wanted to know about selecting the "right" actigraph accelerometer cut-points for youth, but...: A systematic review. *J Sci Med Sport*. 2012;15:311-321
55. Kilner PJ, Geva T, Kaemmerer H, Trindade PT, Schwitter J, Webb GD. Recommendations for cardiovascular magnetic resonance in adults with congenital heart disease from the respective working groups of the european society of cardiology. *Eur Heart J*. 2010;31:794-805
56. Robbers-Visser D, Boersma E, Helbing WA. Normal biventricular function, volumes, and mass in children aged 8 to 17 years. *J Magn Reson Imaging*. 2009;29:552-559
57. Robbers-Visser D, Jan Ten Harkel D, Kapusta L, Strengers JL, Dalinghaus M, Meijboom FJ, Pattynama PM, Bogers AJ, Helbing WA. Usefulness of cardiac magnetic resonance imaging combined with low-dose dobutamine stress to detect an abnormal ventricular stress response in children and young adults after fontan operation at young age. *Am J Cardiol*. 2008;101:1657-1662
58. Robbers-Visser D, Luijnenburg SE, van den Berg J, Roos-Hesselink JW, Strengers JL, Kapusta L, Moelker A, Helbing WA. Safety and observer variability of cardiac magnetic resonance imaging combined with low-dose dobutamine stress-testing in patients with complex congenital heart disease. *Int J Cardiol*. 2011;147:214-218
59. Helbing WA, Luijnenburg SE, Moelker A, Robbers-Visser D. Cardiac stress testing after surgery for congenital heart disease. *Curr Opin Pediatr*. 2010;22:579-586
60. Klitsie LM, Roest AA, Blom NA, Ten Harkel AD. Ventricular performance after surgery for a congenital heart defect as assessed using advanced echocardiography: From doppler flow to 3d echocardiography and speckle-tracking strain imaging. *Pediatr Cardiol*. 2014;35:3-15
61. Koyak Z, Achterbergh RC, de Groot JR, Berger F, Koolbergen DR, Bouma BJ, Lagrand WK, Hazekamp MG, Blom NA, Mulder BJ. Postoperative arrhythmias in adults with congenital heart disease: Incidence and risk factors. *Int J Cardiol*. 2013;169:139-144
62. Eindhoven JA, van den Bosch AE, Jansen PR, Boersma E, Roos-Hesselink JW. The usefulness of brain natriuretic peptide in complex congenital heart disease: A systematic review. *J Am Coll Cardiol*. 2012;60:2140-2149
63. Passino C, Severino S, Poletti R, Piepoli MF, Mammini C, Clerico A, Gabutti A, Nassi G, Emdin M. Aerobic training decreases b-type natriuretic peptide expression and adrenergic activation in patients with heart failure. *J Am Coll Cardiol*. 2006;47:1835-1839
64. Bolger AP, Sharma R, Li W, Leenarts M, Kalra PR, Kemp M, Coats AJ, Anker SD, Gatzoulis MA. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. *Circulation*. 2002;106:92-99



Chapter 2

Systematic review of the effects of physical exercise training programs in children and young adults with congenital heart disease.

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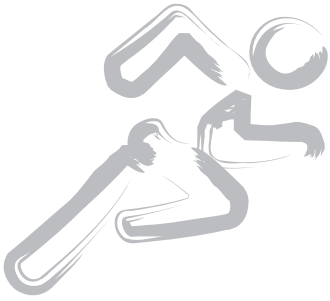


ABSTRACT

Background: Most patients with congenital heart disease (ConHD) do not perform regular physical exercise. Consensus reports have stated that exercise should be encouraged and regularly performed in these patients, but this is not common practice. We reviewed the literature on actual evidence for either negative or positive effects of physical exercise training programs in children and young adults with ConHD.
Methods: Using the Medline database, we systematically searched for articles on physical exercise training programs in ConHD.
Results: A total of 31 articles met all inclusion criteria; in total, 621 subjects (age range 4 to 45 years) were included. Most studies used training programs with duration of 12 weeks. On average, the number of training sessions was 3 times per week. In 12 studies, training intensity was set at a percentage of peak heart rate. Outcome measures reported were peakVO_2, activity levels and muscle strength. Twenty-three studies (72%) found a significant positive change in the main outcome measure after the physical exercise training period. None of the studies reported negative findings related to physical exercise training in ConHD. Cardiac effects have hardly been studied.
Conclusion: In most studies, participation in a physical exercise training program was safe and improved fitness in children and young adults with ConHD. We recommend that patients with ConHD participate in physical exercise training. Cardiac effects need to be studied more extensively.

INTRODUCTION

Most patients with congenital heart disease (ConHD) are less active than healthy peers and do not participate in regular exercise programs[1]. This limited physical activity may be the result of residual hemodynamic problems, chronotropic impairment as well as psychosocial factors such as parental overprotection or restraints imposed by patients' social surroundings[2, 3]. Studies in the field of acquired heart diseases have shown that reduced levels of daily activity are strong predictors of poor outcome, including early death[4]. Physical exercise training programs in patients with acquired cardiovascular disease have resulted in a reduction in mortality and morbidity[5]. Patients with ConHD who participate in sports from an early age on have a significantly lower chance of becoming sedentary adults[6, 7].

European consensus reports in 2006 and 2011 stated that exercise should be performed and encouraged in ConHD patients[8, 9]. Nevertheless, many practitioners are reluctant to recommend exercise for ConHD patients since knowledge of cardiac effects and risks related to exercise is scarce[10].

Furthermore, outcome parameters and predictors for success of exercise programs have not been firmly established. Increased maximal oxygen uptake derived from cardiopulmonary exercise testing (CPET) is commonly used. While this parameter has been shown to be an excellent surrogate marker for long-term outcome in patients with ConHD[11], other factors such as changes in activity level and muscle strength are factors to consider in evaluating the effect of the training programme[12].

Aim of the current review was to assess the negative or positive effects of physical exercise training programs in children and young adults with ConHD.

METHODS

The Medline database was used to search for articles published between 1960 and December 2012 regarding physical in congenital heart disease. The first search term used was: training OR cardiac rehabilitation OR aerobic training OR exercise performance OR exercise training OR rehabilitation OR physical exercise OR physical training OR exercise rehabilitation OR exercise program OR aerobic exercise training OR exercise. The second search term, which could be either in the title or the abstract, was: congenital heart disease OR congenital heart diseases. The search was performed by one of the authors (ND).

The abstracts of relevant articles were screened on the basis of the following criteria: the study population or part of the study population had to have a diagnosed congenital heart disease and intervention had to consist of any type of exercise. If the data in the abstract met the inclusion criteria, the full-text paper was studied. Further reference

lists of articles were checked to retrieve articles that met the inclusion criteria but were not registered in Medline.

The following data was extracted: study design, the nature of ConHD, the nature of any surgery performed; participants' gender, age and age range; the size of the study population and of any control group; the number of drop outs; the type of exercise; the number of training sessions, their duration and locations (home or supervised at an allocated center), and percentage of training sessions which were not performed. The result sections were studied and all results relevant to the training intervention were extracted and interpreted. Results were categorized in adverse events, short-term effects on the heart, on exercise capacity, on muscle strength and activity levels, and on long-term effects on exercise capacity.

RESULTS

The initial search strategy on exercise training produced 191 articles. A total of 31 articles met all inclusion criteria. In these 31 articles 29 study populations were described, of 2 of these populations the short-term and long-term effects were reported in separate articles[13-16]. In this review the 29 study populations are described and analyzed.

Study design and patient population

The study population and design of the included studies is described in table 1. A randomized study design was used 3 times[17-19], a cohort with a control group design 7 times[14, 20-25], a cohort study design 18 times[15, 26-42] and one study was a case report[43]. The age of the subjects in the study ranged from 4 to 45 years. Children were studied in 19 articles[13, 15, 16, 18, 22, 24, 25, 27, 29, 30, 32, 34, 36-40, 42, 44, 45], 4 studies included children and young adults[33, 35, 41, 46] and 6 studies included only adults[17, 19-21, 28, 43].

The number of participants is shown in figure 1. The number of participants in the training group ranged from 1 to 55, with a median of 12. In 14 studies a matched control group of equal size was used[14, 17-25, 27, 29, 37, 46]. Two studies included a control group of healthy volunteers, who participated in the same training programme[40, 41]. Fredriksen et al. created a control group of patients who were interested in participating in the study, but did not want to be placed in the intervention group[24]. Singh et al. and Peja et al. created a control group of patients based on geographic location of the subjects; patients who lived away from the study location formed the control group[24].

Twenty-three studies (79% of all studies) reported their drop-out rate[13,16-21,24,27,28,30,32-37,39-43,45]. Nine(39%) of the studies had no drop-out at all[18, 21, 23, 27, 30, 32, 37, 42, 43]. Overall a median dropout rate of 2 patients (6%) and a range of 0 to 36 participants was noted. The mean percentage of overall training participation, which was reported by 10 studies, was 82%

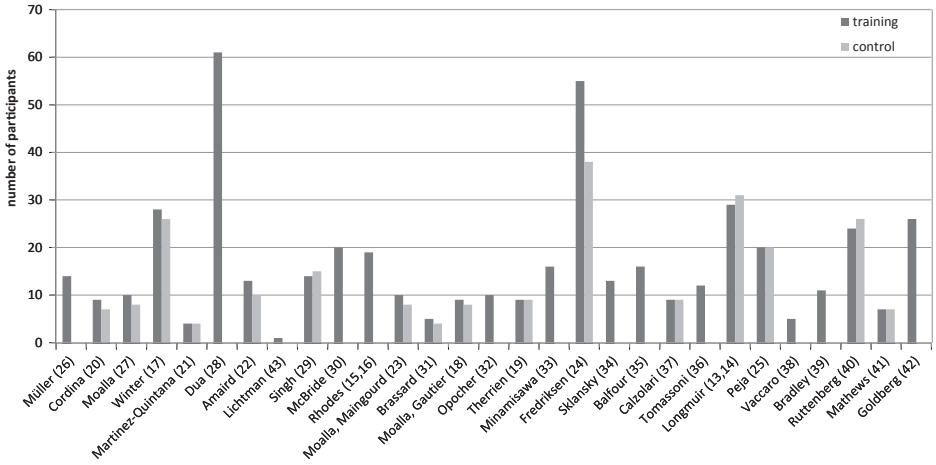


Figure 1: Number of participants

Number of participants per study, if applicable summarized per group. Ordered by year of publication, the oldest publication last.

(range 69-100%)[16, 19, 20, 30, 32, 35, 37, 41-43]. An attendance rate of 100% was only reported by Lichtman et al.[43].

The reported duration of the training programs varied between 6 and 52 weeks. Most studies used training programs with a duration of 12 weeks (n=13 studies)[16, 18, 19, 21, 26, 27, 29, 35-39, 45].

The number of training sessions reported ranged from 1 session per week up to daily training sessions. On average, the number of training sessions per week was 3 times. Five studies added voluntarily training sessions, consisting of the same aerobic exercise training activities used in the supervised training sessions, which were not registered[13, 16, 25, 29, 35]. Fredriksen et al. used two different training schemes: one home-based training scheme with 2 sessions a week, and one center-based training scheme, for which the number of sessions was not stated[24]. Peja et al. divided their participants into groups based on functional status and created a training scheme per group[25].

The exercise time per session ranged between 5 and 60 minutes per session. Nine studies used a range of exercise duration[19, 32, 33, 35, 36, 38-40, 46]. Three studies did not state the duration of the sessions[14, 24, 43]. In one study time per session was incremental, lasting from 5 to 30 minutes per session[28]. One study only specified the duration for a proportion of the participants[25].

Training intensity was set at a percentage of peak heart rate in 12 studies, which was between 50 and 90% of peak heart rate (HR)[17, 21, 24, 34-41, 47]. One study had a set range of HR[25]. The ventilatory threshold level was used as intensity indicator in 5 studies[16, 18, 27, 30, 45]. Three studies used a percentage of peakVO_2[19, 31, 32]. Dyspnea threshold level was used in one study[22]; one other study used the rating of perceived exertion[43]. Peak workload as

Table 1: Study design

Reference	year of publication	Age years Range / mean ± SD	Training Group N	Control Group N	drop out pt /controls (% of all participants)	Overall training not participated %	Duration wk	training/ week n (voluntarily)	Time per session minutes	Training intensity	Training implementation
Müller[26]	2012	4 - 6	14	-	-	-	12	1	60	-	Supervised
Cordina[20]	2012	21 - 41$	9	7‡	3 / 2 (31%)	24 ± 5%	20	3	60	-	Supervised
Moalla[27]	2012	12 - 15	10	8‡	0	-	12	3	60	HR at Vth	Home (HR monitor)
Winter[17]	2011	32 ± 11	28	26‡	4 / 4 (15%)	-	10	3	42	Incremental 60% to 90% PeakHR	Home (HR monitor; weekly email contact)
Martinez-Quintana[21]	2010	18 - 38	4	4‡	0	-	12	2	34 + resistance training	80% PeakHR	Supervised
Dua[28]	2010	32 ± 11	61	0	11 (18%)	-	10	5	5 to 30 min + 10% each week	Based on METS	Home (twice weekly telephone contact)
Amaird[22]	2008	15 ± 1	13	10‡	-	-	8	3	60	DT-level	Home (HR monitor, checked every week)
Lichtman[43]	2008	28	1	0	0	0	-	-	-	RPE driven	Supervised
Singh[29]	2007	12 ± 2	14	15‡	-	-	12	2 (2)	60	-	Home and/or supervised

Table 1 (continued)

Reference	year of publication	Age years Range / mean ± SD	Training Group N	Control Group N	drop out pt /controls (% of all participants)	Overall training not participated %	Duration wk	training/ week n (voluntarily)	Time per session minutes	Training intensity	Training implementation
McBride[30]	2007	14 ± 3	20	0	0	17%	Until HTx (6 ± 4 months)	3	60	HR at Vth and 60% Perceived voluntary contraction	Supervised
Rhodes[15, 16]	2005-06	8 - 16	19	0	3 (16%)	25%	12	2 (2)	60	HR at Vth	Home and/or supervised
Moalla,Maingourd[23]	2006	12 - 15	10	8‡	0	-	12	3	60	HR at Vth	Home (HR monitor)
Brassard[31]	2006	11 - 26	5	4 ‡	-	-	8	3	20 - 30	HR at 50 - 80% PeakVO_2 +resistance training	Home or supervised
Moalla, Gautier[18]	2005	12 - 16	9	8‡	0	-	12	3	60	HR at Vth-level	Home (HR monitor, checked every week)
Opocher[32]	2005	6 - 12	10	0	0	9 pt < 10%; 1 pt > 90%	32	2	30 - 45	50 - 70% PeakVO_2	Home and supervised (HR monitor, monthly telephone contact)
Therrien[19]	2003	25 - 45$	9	9‡	0 / 1 (6%)	20%	12	3	30 - 50	60 - 85% PeakVO_2	Home and supervised (diary)

Table 1 (continued)

Reference	year of publication	Age years Range / mean ± SD	Training Group N	Control Group N	drop out pt /controls (% of all participants)	Overall training not participated %	Duration wk	training/ week n (voluntarily)	Time per session minutes	Training intensity	Training implementation
Minamisawa[33]	2001	19 ± 4	16	0	5 (31%)	-	8 - 12	2 - 3	25 - 36	HR at 60 - 80% PeakHR	Home and/ or supervised (telephone contact)
Fredriksen[24]	2000	10 - 16	55	38 ‡	36 (39%)*	-	2 or 20 **	- / 2 ***	-	65 - 80 % peakHR	Supervised (center or near home)(HR monitor)
Sklansky[34]	1994	6 - 16	13	0	2 (15%)	-	8	3	30	60 - 70% PeakHR	Supervised
Balfour[35]	1991	17 ± 3	16	0	9 (56%)	19%	12	3 (2)	30 - 40	70% PeakHR	Home and supervised
Calzolari[37]	1990	6 - 17	9	9 ‡	0	10%	12	3	60	60 - 70% HRpeak	Supervised
Tomassoni[36]	1990	5 - 15	12	0	4 (33%)	-	12	2 - 3	30 - 60	60 - 80% PeakHR	Home and supervised
Longmuir[13, 14]	1985-90	5 - 14	29	31‡	2 (3%)	-	At least 6£	2 (5)	-	-	Home and supervised (biweekly telephone contact)
Peja[25]	1990	8 ± 4	20	20‡	-	-	52	2 - 3 (-)	45 / -	HR 120 - 150 b/min	Home and supervised
Vaccaro[38]	1987	5 - 12	5	0	-	-	12	2 - 3	30 - 60	60 - 80% PeakHR	Home and supervised

Table 1 (continued)

Reference	year of publication	Age years Range / mean ± SD	Training Group N	Control Group N	drop out pt /controls (% of all participants)	Overall training not participated %	Duration wk	training/ week n (voluntarily)	Time per session minutes	Training intensity	Training implementation
Bradley[39]	1985	4 - 13	11	0	2 (18%)	-	12	2 - 3	25 - 60	60 - 80% PeakHR	Home and supervised
Ruttenberg[40]	1983	7 - 18	24	26 †	12 / 17 (58%)	-	9	3	5 - 30	65 - 75% PeakHR	Supervised
Mathews[41]	1983	12 - 20	7	7 †	3 / 3 (43%)	18%	52	3	50	75 - 80% peakHR	Supervised
Goldberg[42]	1981	14 ± 3	26	0	0	31%	6	3 - 4	45	50 - 70% PeakWL	Home (diary and weekly telephone contact)

HR heart rate; Vth Ventilatory threshold; HTx heart transplantation; RPE rating perceived exertion; DT dyspnea threshold; PeakVO_2Ventilatory Oxygen: PeakWL workload peak; b/min beats per minute. ‡ control group consists of subjects with a ConHD who do not train; † control group consists of healthy subjects who do train;* 38 patients were excluded after enrolment, it is not mentioned in which group they participated;**. 2 weeks training in rehabilitation center or 20 weeks training in a home based center; *** training per week not mentioned in rehabilitation center based study; $ article defines age per category: Cordina: training group 31±10, control group 33±2; Therrien: training group 35±10, control group 33±7;£ rehabilitation program starts in hospital after surgery, period is not defined, after discharge the program continues for 6 weeks at home.

a guideline for physical exercise training was used in one study[42]; and one study based intensity on METS[28].

Seven studies used a home based physical exercise programme[17, 18, 22, 23, 27, 28, 42]. All home based studies used a monitoring system (heart rate monitor, email or telephone

Table 2: Distribution of types of congenital heart disease in the populations in the studies included

Reference	ToF (n)	Fontan (n)	TGA (n)	Left obstructive lesions (n)	Right obstructive lesions (n)	L-R shunts (n)	Other (n)	Total
Müller[26]	2	1	1	4	3	3		14
Cordina[20]		11						11
Moalla[27]	5	4	5			4		18
Winter[17]		54						54
Martinez-Quintana[21]		4*	2*			1*		7
Dua[28]	8	4	5	10	3	7	13	50
Amiard[22]	5		5			5	8	23
Lichtman[43]		1						1
Singh[29]		11					3	14
Mcbride[30]		4					16	20
Rhodes[15, 16]		11	1		2	1	1	16
Moalla,Maingourd[23]	5	4	5			4		18
Brassard[31]		7						7
Moalla, Gautier[18]	4	4	7			2		17
Opocher[32]		10						10
Therrien[19]	17							17
Minamisawa[33]		16						16
Fredriksen[24]	16	17	6	20	9	16	9	93
Sklansky[34]	11							11
Balfour[35]	1	2		3	1	2	7	16
Calzolari[37]	9							9
Tomassoni[36]	2	2	3				1	8
Longmuir[13, 14]	3			19	1	25	12	60
Peja[25]	5			7	3	25		40
Vaccaro[38]			5					5
Bradley[39]	4		5					9
Ruttenberg[40]	10	2	3	9				24
Mathews[41]	3			2	1		1	7
Goldberg[42]	16					10		26
TOTAL	126	169	53	74	23	105	71	621

ToF tetralogy of Fallot; TGA Transposition of the great arteries; R-L shunts: right to left shunts; Prim HT: primary pulmonary hypertension; * pulmonary hypertension present; # only the patients which completed the study are presented.

contact). Training was supervised in 10 studies[20, 21, 24, 30, 34, 37, 40, 41, 43, 44]. All other studies used a combination of home-based training and supervised training[13, 16, 19, 25, 29, 31-33, 35, 36, 38, 39].

Table 2 provides an overview of the different types of ConHD included in the studies. Patients with known arrhythmias and patients with significant residual obstructive lesions were not included in any of the studies.

Patients with Fontan circulation have been included as univentricular heart patients, regardless of their underlying pathology. Patients with transposition of the great arteries (TGA) corrected with either a Senning or Mustard operation were grouped together.

Ten studies included patients from a single diagnosis category[17, 19, 20, 32-34, 37, 38, 43, 46]; 6 included Fontan patients[17, 20, 32, 33, 43, 46], 3 included tetralogy of Fallot (ToF) patients[19, 34, 37], and 1 included patients with TGA[38]. In total, 621 subjects were included, 169 (27%) patients with Fontan circulation, 126 (20%) ToF patients, 53 (9%) TGA patients, 74 (12%) with a left obstructive lesion, 23 (4%) with a right obstructive lesion, 105 (17%) with a left to right shunt and 71 (11%) subjects who had a heart defect which did not fit the previous categories.

Short-term effects of training programs

Table 3 shows the methods used to assess the effects of the intervention.

Adverse events

Eighteen studies reported on the occurrence of adverse events. Thirteen did not report any adverse event[16, 18, 22, 27, 28, 30, 33, 34, 36, 38, 39, 43, 45]. In the other 5, an adverse event occurred[17, 19, 20, 30, 41]. In the study of Mathews, 1 patient with known ventricular arrhythmias died in circumstances not related to exercise[41]. One patient experienced a transient ischemic attack, 2 patients had seizures[30,20]. None of these events were related to exercise and/or training sessions. In 1 patient ventricular bigeminy was noted at the baseline ergometry test. This patient was excluded from the study, in concordance with the inclusion criteria[17]. One study mentioned occasional premature ventricular and atrial beats[19]. None of these patients were withdrawn from the studies. No one experienced sudden cardiac death during exercise.

Effects on the heart

Ten of the 29 studies measured the effect of an exercise program on the heart. One study used cardiac MRI to assess ejection fraction, stroke volume and valvular regurgitation[20], 2 studies measured NT-proBNP[17, 21], and all other studies assessed potential ECG-changes as a result of physical exercise training. Improvements in ventricular filling and cardiac output were demonstrated using MRI. NT-proBNP did not change after training. There were no ECG changes due to physical exercise training.

Table 3: Outcome regarding cardiac status, adverse outcomes and parameters of reported training programs

Reference	Test method cardiac status	Cardiac status and/or adverse outcome	Test method outcome parameter	Outcome
Müller[26]	-		-MOT 4 - 6 from Zimmer et al (gives motor quotient)	-Slightly increase of motor quotient in whole group; significant increase in subgroup who had a less than normal motor quotient at baseline
Cordina[20]	-Cardiac MR	-Improvements in cardiac filling and cardiac output; as well as reduced dependence on respiration for blood return to the heart via IVC -One transient ischemic event (not during training); no arrhythmia or other reported cardiac events	-Strength test -CPET, bicycle ramp-protocol, maximal test -Total body DXA -Calf MRS	-Strength increased by 43 ± 7% -Significant increase in PeakVO_2 (Δ 183 ± 31 ml/min) in training group; after 12-month detrained period a decrease of 0,5 l/min -A significant increase of total body lean mass and non-dominant calf lean mass in training group (Δ1,94 ± 0.52 kg); after 12-month detrained period a decrease of 3.2 kg - No significant change in calf MRS
Moalla[27]	-	-All tests were well tolerated without major complaints or complication	-Isokinetic dynometer (MVC and T_{lim}) -NIRS over vastus lateralis muscle	-MVC and T_{lim} significant increased in training group -Significant improved use of oxygen and significantly faster reoxygenation in training group -Both outcomes are highly correlated (r = 0.95)
Winter[17]	-NT-proBNP	-No significant changes -One patient developed ventricular bigeminy in recovery phase of exercise test and was excluded from the study -One patient sustained calf injury and discontinued the protocol for 2 weeks	-CPET, bicycle ramp-protocol, maximal test -QoL (SF-36 and CHD-TAAQOL)	-Significant increase in peakVO_2 and a significant improvement of OUES; both in the training group -No changes in QoL
Martinez-Quintana[21]	-NT-proBNP	-No significant changes	–6MWT -Pedometer -Hand grip strength -Isometric strength of the quadriceps -QoL (SF-12 V_2)	-No significant change in either of the mentioned tests -Although no endpoint, a perceived improvement, of 1 NYHA class was noted in the training group

Table 3 (continued)

Reference	Test method cardiac status	Cardiac status and/or adverse outcome	Test method outcome parameter	Outcome
Dua[28]	-ECG -Echocardiogram	-No mention of ECG or echocardiogram outcomes -No death or adverse effects	-CPET, treadmill standard Bruce protocol, maximal test -QoL (PAQ, SF-12, SWLS and PSPP-scf) -Accelerometer (Actigraph and Caltrac)	-Median duration of treadmill exercise time significant increased -All questionnaires used to assess QoL showed a significant increase -Significant increase of mean moderate-to-vigorous-physical-activity; activity associated energy expendure increased significantly
Amiard[22]	-	-No trail was interrupted for angina, ST depression, arrhythmia or hypertension	-CPET, bicycle ramp-protocol, maximal test	-Non-significant improvement in aerobic capacity
Lichtman[43]	-	-Remained in sinus rhythm	-CPET, treadmill Modified Bruce protocol, maximal test -QoL (SF-36)	–15% improvement duration of treadmill exercise time; 26% increase of PeakVO_2 (ml/kg/min) • 68% decrease in depression scale (CES-D in SF-36)
Singh[29]	-		-CPET, bicycle ramp-protocol, maximal test	• Significant improvement of PeakVO_2(ml/kg/min) in training group; significant improvement of 1 and 3-minute HR recovery in training group; PeakVO_2 and 3-minute HR recovery was sustained during 4-10 months follow-up
Mcbride[30]	-Telemetry during exercise -Blood pressure measurements	–2 seizures occurred, neither resulting in termination of the programme -No adverse episodes of hypotension or significant arrhythmias occurred	-	-
Rhodes[15, 16]	-	-No rehabilitation-related complication occurred	-CPET, bicycle ramp-protocol, maximal test	-Significant improvement in PeakVO_2 and Peak Work rate, which is sustained during the follow-up period of 7±2 months
Moalla, Maingourd[23]	-	-No major complaint or complication	-CPET, bicycle ramp-protocol, maximal test -NIRS over respiratory muscles -Pulmonary test	-Significant improvement at Vth of VO_2, workload and HR, not significant at peak -Significant less deoxygenation in respiratory muscle indicating improvement of tissue oxygenation -No significant changes in pulmonary test
Brassard[31]	-	-	-CPET, bicycle ramp-protocol, maximal test -Neuromuscular functioning	-No change in peak VO_2 -Non-significant positive influence on neuromuscular function

Table 3 (continued)

Reference	Test method cardiac status	Cardiac status and/or adverse outcome	Test method outcome parameter	Outcome
Moalla, Gautier[18]	-	-No symptoms or clinical complications occurred	–6MWT -CPET, bicycle ramp-protocol, maximal test	-Significant improvement of walking distance in 6MWT -Non-significant improvement of peakVO_2 and peak workload
Opocher[32]	-	-	-CPET, treadmill Bruce protocol, maximal test	-Significant improvement of METs' ratio, and PeakVO_2 after exclusion of non-compliant subject
Therrien[19]	-	-No death or morbid events -Occasional premature ventricular and atrial beats	-CPET, bicycle ramp-protocol, maximal test	-Significant improvement of PeakVO_2
Minamisawa[33]	-	-No adverse cardiovascular events occurred	-CPET, bicycle ramp-protocol, maximal test	-Significant improvement of peakVO_2, PeakWorkload and exercise time
Fredriksen[24]	-	-	-CPET, treadmill Oslo protocol, maximal test -Activity monitor -QoL (YSR and CBC)	-Both (training and control) group significant increase in PeakVO_2, not significant increase in training group corrected for weight -Significant increase in activity in training group -Marked increased social effect in both groups
Sklansky[34]	-Echocardiography –24 hour ECG	-No significant echocardiac changes -No significant changes in 24 hour ECG registration	-CPET, treadmill Bruce protocol, maximal test -Single-stage submaximal exercise protocol	-Significant improvement of treadmill time; significant decrease of submaximal HR and VO_2, indicating an improved exercise economy -No significant trainings effect in submaximal exercise test
Balfour[35]	-Patients at risk of dysrhythmias had a telemetry for 3 sessions	-No mention of telemetry results	-CPET, treadmill Bruce protocol, maximal test	-Significant improvement of exercise time and PeakVO_2
Calzolari[37]	-	-	-CPET, bicycle James-protocol, maximal test -Submaximal exercise; treadmill	-Non-significant improvement in exercise time and PeakWorkload -Significant improvement of treadmill time at the submaximal exercise test
Tomassoni[36]	-Single lead-ECG during each training session	-No significant change ST depression	-CPET, treadmill Modified Bruce protocol, maximal test	-Significant improvement of exercise time and cardiac output

Table 3 (continued)

Reference	Test method cardiac status	Cardiac status and/or adverse outcome	Test method outcome parameter	Outcome
Longmuir[13, 14]	-	-	–7 test to assess cardiovascular endurance, strength, flexibility and coordination (based on Canada Fitness Award test)	-Significant improvement in the area of cardiovascular endurance in the compliant sport group; maintenance of the improvement during follow-up -Significant improvement in the area of strength, flexibility and coordination in the compliant sport group; maintenance of the improvement during follow-up
Peja[25]	-	-	-CPET; bicycle, submaximal test	-Significant improvement in physical working capacity at HR 170 b/min
Vaccaro[38]	-ECG each training session	-No significant change ST depression	-CPET, treadmill maximal test	-Increase in PeakVO_2 and treadmill time
Bradley[39]	-Single lead-ECG during each training session	-No complications	-CPET, treadmill Modified Bruce protocol, maximal test	-Significant improvement of treadmill time and PeakVO_2
Ruttenberg[40]	-	-	-CPET, treadmill Bruce protocol, maximal test	-Significant improvement of PeakVO_2 and PeakWorkload in the group of left obstructive lesions; significant improvement of PeakWorkload in the TGA group
Mathews[41]	-	-One patient with known ventricular arrhythmia died during eating	-CPET, treadmill Balke protocol, maximal test –7 psychological evaluations -Lipid analysis	-Three of the 4 subjects increased to normal values of PeakVO_2 -Overall psychological improvement -Reduction in serum cholesterol
Goldberg[42]	-	-	-CPET; bicycle, maximal test	-Significant increase in PeakWorkload -Significant decrease of submaximal HR and VO_2, indicating an improved exercise economy

CPET: cardiopulmonary exercise test; DXA dual-energy X ray; MRS muscle phosphorus spectroscopy; MVC: maximal voluntary contraction; T_{lim}: time to exhaustion (limit time) QoL: quality of life; 6MWT: six minutes walk-test; PAQ physical activity (self-efficacy) questionnaire; SWLS: satisfaction with life scale; PSPP-scf: physical self-perception pro file-short clinical form; CES-D center for epidemiologic studies depression scale; IVC: inferior vena cava; YSR: youth self-report; CBC: child behavior checklist.

Twenty-two studies found a statistically significant positive effect in their training group after the physical exercise training[13-20, 23-29, 32-40, 42]. Sixteen studies of those involved only children (in total 19 studies with only children), 2 studies had a population of children and young adults (in total 4 studies with a mixed population) and 4 studies involved only adults (in total 6 studies with only adults).

Seven studies did not show any positive effect in their training group after the physical exercise training[21, 22, 30, 38, 41, 43, 46]. In case of the study by McBride et al., the safety of an inpatient physical exercise training program in pediatric patients awaiting heart transplantation while on inotropic support was the main aim, rather than the effects on fitness[30]. Six studies concluded that they were inadequate to assess physical exercise training effects, for reasons of small sample size and/or a training period that was too short[22 21, 31 38, 41, 43]. Three of the studies that did not show any significant effect of the exercise intervention involved only children (from a total 19 studies with only children)[22, 30, 38], 2 studies had a mixed population of children and young adults (from a total of 4 studies with a mixed population)[31, 41] and 2 studies involved only adults (from 6 studies with adults only)[21, 43].

Effects on exercise capacity

Twenty-four studies used a maximal exercise test to assess the training effect, either by graded cycle ergometry (13 studies)[15, 17-20, 22, 23, 25, 29, 31, 33, 37, 42] or by treadmill[24, 28, 32, 34-36, 38-41, 43]. The Bruce protocol, modified or standard was used most frequently. In figure 2 the peakVO_2 changes from those studies are shown. Mean baseline peakVO_2 was 32,2 ml/kg/min. The mean increase after the training period (for 177 participants) in peakVO_2 was 2.6 ml/kg/min. Twelve studies showed a statistically significant increase in peakVO_2 in the training group[15, 17, 19, 20, 24, 29, 32, 33, 35, 38-40]. Two studies that did not show any significant change at peakVO_2 showed a significant increase in VO_2 at ventilatory threshold[18, 23], another two studies reported a significant decrease in submaximal VO_2, indicating improved exercise economy[34, 41]. Three studies did not report any significant increase in either peakVO_2, nor in other VO_2 related parameters[22, 31, 43]. These 3 studies had a small sample size.

The six minute walk-test was used in 2 studies, once as an addition to the CPET, once as the only assessment of the training effect[18, 21]. Moalla et al. showed a significant improvement of walking distance[18] (in concordance with a significant increase in VO_2 at Vth), Martinez-Quintana did not show a significant improvement, as their study population was most likely too small[21].

Effects on muscle strength

Five studies reported on muscle-strength. Three reported a statistically significant increase in strength[14, 20, 27], Muller et al. reported an increase in the subset who had a less than normal motor quotient at baseline[26] and one reported no change[21], most likely due to the small study population.

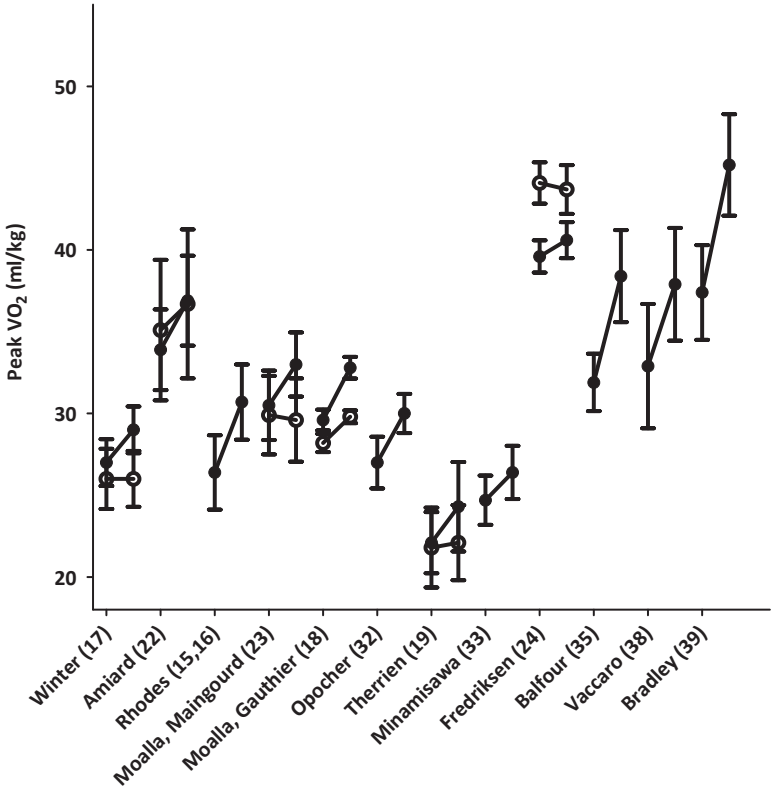


Figure 2: Peak VO2 changes
Peak VO2 values measured before and after the intervention. Closed rounds are the intervention groups, and were applicable open rounds are the control groups.

Effects on activity level

Two studies measured change in activity level, both found a significant increase in physical activity after training[24, 28].

Long-term effects

Four studies re-assessed the training group after cessation of the training program. Longmuir et al. retested the training group at 6 months post-training. The improvement in exercise capacity as measured directly after the training program was sustained[13]. Rhodes et al. retested their training group after 5 to 9 months. They noted that the exercise function was sustained as well[15]. Singh et al. retested their training group subjects after 4 to 10 months. They noted a sustained improved 3-minute heart rate recovery[29]. Mathews et al. noted a loss of training effect 6 months post training[41].

DISCUSSION

Aim of the current review was to assess the negative or positive effects of physical exercise training programs in children and young adults with ConHD. We found that most studies showed a significant positive effect of physical exercise training.

The majority of studies have been performed in pediatric populations. Sixteen out of the 19 studies in this age group showed a significant improvement of physical parameters. In the adult population 4 out of 6 studies showed the same effect. Four studies used a mixed population of children and adults. Significant improvement of physical parameters was noted in 2 of these studies. Since the success rates in the different age groups were not equal and the number of observations is relatively small we cannot draw firm conclusions on potential age related differences of physical exercise training programs. Training effects in children with ConHD have been documented best[48].

Although some serious adverse events have been reported (in 4 out of 621 patients), from the description of these events it is unlikely they were related to the exercise program, or to the patients underlying condition. None of the studies reported sudden cardiac death. Generally, there is little evidence that physical exercise training as described in the studies included in this review is not safe for patients with ConHD. It should be acknowledged that most studies excluded patients with sustained arrhythmias and severe obstruction to ventricular outflow. These are generally accepted contra-indications to perform physical exercise in patients with ConHD[49].

Few studies have examined the direct effects of physical exercise training on the heart or vasculature. Pro-arrhythmic ECG changes have not been observed, suggesting that exercise training does not increase the risk of arrhythmia in patients with ConHD. Only one study used an imaging technique (MRI) to assess cardiac effects and noted an improvement in ejection fraction and stroke volume. This is in line with findings in healthy individuals showing enhanced SV after a period of exercise training[50]. In patients with acquired heart disease positive cardiac outcomes have been reported. These benefits include improved left ventricular ejection fraction, favorable remodeling of the left ventricle, enhanced endothelial function and augmented regenerative capacity of circulating progenitor cells[5, 51, 52]. These effects have not been studied in patients with congenital heart disease in relation to exercise training. The relative lack of data on cardiac effects is remarkable and deserves further attention.

On average, physical exercise training resulted in a mean peakVO_2 increase of 2.6 ml/kg/min, which is an average increase of ± 8% of peakVO_2. This is in line with the effects of exercise training in patients with acquired heart failure[5]. Maximal values are difficult to obtain, especially in the pediatric age group. Submaximal exercise measurements have been assessed in very limited number of studies. In the single study that used the slope of the VE/VCO_2 slope relationship, no significant change was noted.[31]. Winter et al.

reported the oxygen uptake efficiency slope (OUES), which did not change significantly after training[17]. Three studies reported VO_2 at ventilatory threshold, and demonstrated a significant increase after physical exercise training[15, 18, 23]. This suggests that oxygen delivery and consumption has improved and consequently the threshold for anaerobic metabolism has been shifted upward by exercise training.

Muscle strength was included in five studies, that all used different methods. The studies that were not underpowered showed a significant increase in muscle strength[14, 20, 26, 27]. Since muscle strength is an important parameter for functional daily life activities, the improved muscle strength will benefit the patient[53].

The two studies that measured activity levels found a significant increase in those levels after training. Although based on limited data, physical exercise training might get patients more active and therefore less prone to a sedentary life with a reduced risk of cardiovascular disease associated with a sedentary life-style[3].

The differences in reported outcome measures such as oxygen uptake, activity level, muscle strength, submaximal performance, underline the lack of consensus on outcome measures for the physical exercise training in this population[48]. We recommend establishing a core-set of outcome measures to improve the benchmarking of different training protocols.

The large majority of the studies used dynamic submaximal exercise as the basis of the training program. A different approach of was taken by Cordina et al. They used strength training to study cardiac changes and concluded that strength training, if performed without the Valsalva maneuver, is safe and may reduce the respiratory dependency in Fontan patients[20]. This questions the 'no strength training' dogma that is commonly applied in ConHD[48].

Failure to demonstrate training effects was commonly associated with a limited duration of the training program and/or small sample sizes[22]. Over-all, the drop-out rate was low and participation in training was adequate. In general, significant positive effects of physical exercise training programs were reported for those patients who trained for at least 8 weeks. The variation of duration of time per exercise session was limited, preventing clear conclusions on this factor. However, within the limits used (30-60 minutes), the duration of time per session did not seem to have an important influence on the general effect of the training program. All studies used steady state designs. Interval training has been uncommon. Training intensity has been based on percentages of peakHR, peakVO_2 or ventilatory threshold. The available studies do not allow a conclusion on the most optimal training intensity. Training location had been considered an important factor in the sustainability of physical exercise training programs. In the studies we evaluated, home-based programs without direct supervision, supervised exercise in a center, or combination of both were used. There was no clear difference in outcomes depending on these strategies, therefore we concluded that both the center based as well as the home base training programs are feasible.

An important question is whether there could be differences in trainability between different diagnostic categories. Of the 6 studies that included only Fontan patients, 4 showed a significant effect[17, 20, 32, 33]. The studies in Fontan patients that did not reach significant improvement most likely were underpowered due to small sample size[31, 43]. In the 3 studies that included ToF patients exclusively, a significant effect on exercise capacity was noted in all[19, 34, 37]. Most studies included a range of different types of ConHD. Often this resulted in sample sizes that were too small to perform sub analyses per diagnostic category of ConHD. Therefore it remains unclear if a difference in trainability exists between different ConHD types. The extent of residual abnormalities may have an important impact on the exercise performance and thereby on the result of a physical exercise training program. For instance, patients with a Fontan circulation may have reduced vasodilator response or chronotropic impairment[54]. Fontan patients with chronotropic incompetence may have more exercise limitation than those with chronotropic competence[30].

Long-term sustainability of training programs is an important goal. Data in this review were limited. Only 4 studies described the long-term effects, measured up to 10 months after the exercise program. Three out of these 4 reported a sustained effect of improvement in exercise capacity.[13, 16, 29]. These results provide evidence for a long-term sustainability of improved exercise capacity. Consensus is lacking on optimal strategies to obtain sustained effects. This needs further study.

Reluctance of physicians to refer patients with ConHD to exercise programs has been suggested to be among the reasons for low participation in exercise programs of these patients. This reluctance may in part reflect the limited data on potential cardiac adverse effects of exercise in these patients. The effects of physical exercise training in ConHD with regard to fitness have been documented, as discussed in the current review. However, the lack of studies documenting the direct effect on the heart of such training programs is striking.

Based on the findings of the current review, we recommend that future studies should be designed with at least 9 weeks of training supervised in person or by adequate monitoring tools. Future studies should have sufficient power to demonstrate effects of training schemes, in well-defined homogeneous study populations, with adequately randomized intervention and control groups. The design should allow measurements on exercise improvement, activity levels and motor function, as well as on cardiac changes due to training. Furthermore, items that need to be addressed in future studies are proper outcome measures for the assessment of training programs in congenital heart disease, the most adequate type of exercise, the duration and intensity of individual training sessions and of the entire training program, the trainability of patients depending on underlying diagnosis, and the effects of the training location, particularly with regard to the long-term sustainability of the effect on exercise performance.

In conclusion, most studies in this review showed that in children and young adults with ConHD exercise is safe and an improvement of fitness after a physical exercise training program can be obtained, despite large variation in training schemes, the type of supervision of training and outcome measures. There is a lack of knowledge of the effect of exercise training on individual diagnostic categories and on the heart itself. This review supports that physical exercise training should be part of the care of congenital heart disease treatment as suggested previously in consensus reports[8, 9].

REFERENCES

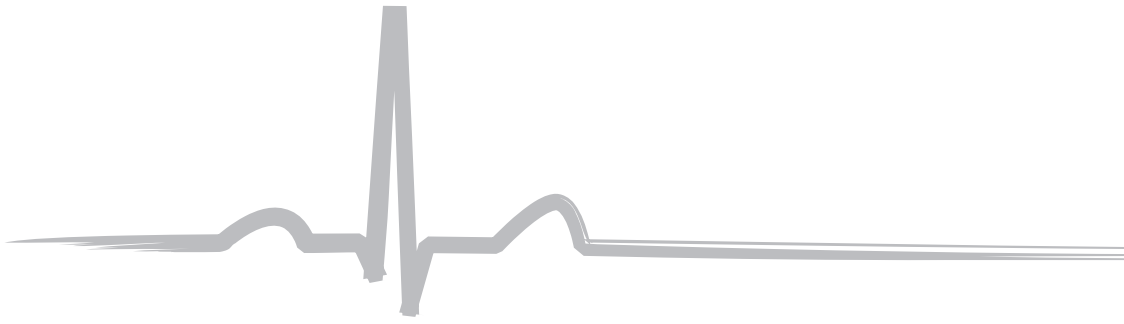
1. Dua JS, Cooper AR, Fox KR, Graham Stuart A. Physical activity levels in adults with congenital heart disease. *Eur J Cardiovasc Prev Rehabil*. 2007;14:287-293
2. Belardinelli R, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: Effects on functional capacity, quality of life, and clinical outcome. *Circulation*. 1999;99:1173-1182
3. Reybrouck T, Mertens L. Physical performance and physical activity in grown-up congenital heart disease. *Eur J Cardiovasc Prev Rehabil*. 2005;12:498-502
4. Walsh JT, Charlesworth A, Andrews R, Hawkins M, Cowley AJ. Relation of daily activity levels in patients with chronic heart failure to long-term prognosis. *Am J Cardiol*. 1997;79:1364-1369
5. Piepoli MF, Davos C, Francis DP, Coats AJ, ExTra MC. Exercise training meta-analysis of trials in patients with chronic heart failure (extramatch). *BMJ*. 2004;328:189
6. Moola F, McCrindle BW, Longmuir PE. Physical activity participation in youth with surgically corrected congenital heart disease: Devising guidelines so johnny can participate. *Paediatr Child Health*. 2009;14:167-170
7. Schickendantz S, Sticker E, Dordel S, Bjarnason-Wehrens B. Sport and physical activity in children with congenital heart disease. *dtsch Arztebl*. 2007;104:6
8. Takken T, Giardini A, Reybrouck T, Gewillig M, Hovels-Gurich HH, Longmuir PE, McCrindle BW, Paridon SM, Hager A. Recommendations for physical activity, recreation sport, and exercise training in paediatric patients with congenital heart disease: A report from the exercise, basic & translational research section of the european association of cardiovascular prevention and rehabilitation, the european congenital heart and lung exercise group, and the association for european paediatric cardiology. *Eur J Prev Cardiol*. 2012;19:1034-1065
9. Hirth A, Reybrouck T, Bjarnason-Wehrens B, Lawrenz W, Hoffmann A. Recommendations for participation in competitive and leisure sports in patients with congenital heart disease: A consensus document. *Eur J Cardiovasc Prev Rehabil*. 2006;13:293-299
10. Longmuir PE, McCrindle BW. Physical activity restrictions for children after the fontan operation: Disagreement between parent, cardiologist, and medical record reports. *Am Heart J*. 2009;157: 853-859
11. Giardini A, Specchia S, Tacy TA, Coutsoumbas G, Gargiulo G, Donti A, Formigari R, Bonvicini M, Picchio FM. Usefulness of cardiopulmonary exercise to predict long-term prognosis in adults with repaired tetralogy of fallot. *Am J Cardiol*. 2007;99:1462-1467
12. Kempny A, Dimopoulos K, Uebing A, Moceri P, Swan L, Gatzoulis MA, Diller GP. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life--single centre experience and review of published data. *Eur Heart J*. 2012;33:1386-1396
13. Longmuir PE, Tremblay MS, Goode RC. Postoperative exercise training develops normal levels of physical activity in a group of children following cardiac surgery. *Pediatr Cardiol*. 1990;11:126-130
14. Longmuir PE, Turner JA, Rowe RD, Olley PM. Postoperative exercise rehabilitation benefits children with congenital heart disease. *Clin Invest Med*. 1985;8:232-238
15. Rhodes J, Curran TJ, Camil L, Rabideau N, Fulton DR, Gauthier NS, Gauvreau K, Jenkins KJ. Impact of cardiac rehabilitation on the exercise function of children with serious congenital heart disease. *Pediatrics*. 2005;116:1339-1345
16. Rhodes J, Curran TJ, Camil L, Rabideau N, Fulton DR, Gauthier NS, Gauvreau K, Jenkins KJ. Sustained effects of cardiac rehabilitation in children with serious congenital heart disease. *Pediatrics*. 2006; 118:e586-593

17. Winter MM, van der Bom T, de Vries LC, Balducci A, Bouma BJ, Pieper PG, van Dijk AP, van der Plas MN, Picchio FM, Mulder BJ. Exercise training improves exercise capacity in adult patients with a systemic right ventricle: A randomized clinical trial. *Eur Heart J*. 2012;33:1378-1385
18. Moalla W, Gauthier R, Maingourd Y, Ahmaidi S. Six-minute walking test to assess exercise tolerance and cardiorespiratory responses during training program in children with congenital heart disease. *Int J Sports Med*. 2005;26:756-762
19. Therrien J, Fredriksen P, Walker M, Granton J, Reid GJ, Webb G. A pilot study of exercise training in adult patients with repaired tetralogy of fallot. *Can J Cardiol*. 2003;19:685-689
20. Cordina RL, O'Meagher S, Karmali A, Rae CL, Liess C, Kemp GJ, Puranik R, Singh N, Celermajer DS. Resistance training improves cardiac output, exercise capacity and tolerance to positive airway pressure in fontan physiology. *Int J Cardiol*. 2013;168:780-788
21. Martinez-Quintana E, Miranda-Calderin G, Ugarte-Lopetegui A, Rodriguez-Gonzalez F. Rehabilitation program in adult congenital heart disease patients with pulmonary hypertension. *Congenit Heart Dis*. 2010;5:44-50
22. Amiard V, Jullien H, Nassif D, Bach V, Maingourd Y, Ahmaidi S. Effects of home-based training at dyspnea threshold in children surgically repaired for congenital heart disease. *Congenit Heart Dis*. 2008;3:191-199
23. Moalla W, Maingourd Y, Gauthier R, Cahalin LP, Tabka Z, Ahmaidi S. Effect of exercise training on respiratory muscle oxygenation in children with congenital heart disease. *Eur J Cardiovasc Prev Rehabil*. 2006;13:604-611
24. Fredriksen PM, Kahrs N, Blaasvaer S, Sigurdsen E, Gundersen O, Roeksund O, Norgaand G, Vik JT, Soerbye O, Ingjer E, Thaulow E. Effect of physical training in children and adolescents with congenital heart disease. *Cardiol Young*. 2000;10:107-114
25. Peja M, Boros A, Toth A. [effect of physical training on children after reconstructive heart surgery]. *Orv Hetil*. 1990;131:2085-2086, 2089-2090
26. Muller J, Pringsheim M, Engelhardt A, Meixner J, Halle M, Oberhoffer R, Hess J, Hager A. Motor training of sixty minutes once per week improves motor ability in children with congenital heart disease and retarded motor development: A pilot study. *Cardiol Young*. 2012:1-5
27. Moalla W, Elloumi M, Chamari K, Dupont G, Maingourd Y, Tabka Z, Ahmaidi S. Training effects on peripheral muscle oxygenation and performance in children with congenital heart diseases. *Appl Physiol Nutr Metab*. 2012;37:621-630
28. Dua JS, Cooper AR, Fox KR, Graham Stuart A. Exercise training in adults with congenital heart disease: Feasibility and benefits. *Int J Cardiol*. 2010;138:196-205
29. Singh TP, Curran TJ, Rhodes J. Cardiac rehabilitation improves heart rate recovery following peak exercise in children with repaired congenital heart disease. *Pediatr Cardiol*. 2007;28:276-279
30. McBride MG, Binder TJ, Paridon SM. Safety and feasibility of inpatient exercise training in pediatric heart failure: A preliminary report. *J Cardiopulm Rehabil Prev*. 2007;27:219-222
31. Brassard P, Poirier P, Martin J, Noel M, Nadreau E, Houde C, Cloutier A, Perron J, Jobin J. Impact of exercise training on muscle function and ergoreflex in fontan patients: A pilot study. *Int J Cardiol*. 2006;107:85-94
32. Opocher F, Varnier M, Sanders SP, Tosoni A, Zaccaria M, Stellin G, Milanesi O. Effects of aerobic exercise training in children after the fontan operation. *Am J Cardiol*. 2005;95:150-152
33. Minamisawa S, Nakazawa M, Momma K, Imai Y, Satomi G. Effect of aerobic training on exercise performance in patients after the fontan operation. *Am J Cardiol*. 2001;88:695-698

34. Sklansky MS, Pivarnik JM, O'Brian Smith E, Morris J, Bricker JT. Exercise training hemodynamics and the prevalence of arrhythmia's in children following tetralogy of fallot repair. *Pediatric Exercise Science*. 1994;6:188-200
35. Balfour IC, Drimmer AM, Nouri S, Pennington DG, Hemkens CL, Harvey LL. Pediatric cardiac rehabilitation. *Am J Dis Child*. 1991;145:627-630
36. Tomassoni TL, Galioto FM, Jr., Vaccaro P, Vaccaro J. Effect of exercise training on exercise tolerance and cardiac output in children after repair of congenital heart disease. *Sports Training, Med and Rehab*. 1990;2:57-62
37. Calzolari A, Turchetta A, Biondi G, Drago F, De Ranieri C, Gagliardi G, Giambini I, Giannico S, Kofler AM, Perrotta F, et al. Rehabilitation of children after total correction of tetralogy of fallot. *Int J Cardiol*. 1990;28:151-158
38. Vaccaro P, Galioto FM, Jr., Bradley LM, Vaccaro J. Effect of physical training on exercise tolerance of children following surgical repair of d-transposition of the great arteries. *J Sports Med Phys Fitness*. 1987;27:443-448
39. Bradley LM, Galioto FM, Jr., Vaccaro P, Hansen DA, Vaccaro J. Effect of intense aerobic training on exercise performance in children after surgical repair of tetralogy of fallot or complete transposition of the great arteries. *Am J Cardiol*. 1985;56:816-818
40. Ruttenberg HD, Adams TD, Orsmond GS, Conlee RK, Fisher AG. Effects of exercise training on aerobic fitness in children after open heart surgery. *Pediatr Cardiol*. 1983;4:19-24
41. Mathews RA, Nixon PA, Stephenson RJ, Robertson RJ, Donovan EF, Dean F, Fricker FJ, Beerman LB, Fischer DR. An exercise program for pediatric patients with congenital heart disease: Organizational and physiologic aspects. *J Cardiac Rehabil*. 1983;3:467-475
42. Goldberg B, Fripp RR, Lister G, Loke J, Nicholas JA, Talner NS. Effect of physical training on exercise performance of children following surgical repair of congenital heart disease. *Pediatrics*. 1981;68: 691-699
43. Lichtman SW, Caravano M, Schneyman M, Howell B, King ML. Successful outpatient cardiac rehabilitation in an adult patient post-surgical repair for tricuspid valve atresia and hypoplastic right ventricle: A case study. *J Cardiopulm Rehabil Prev*. 2008;28:48-51
44. Muller J, Hess J, Hager A. Daily physical activity in adults with congenital heart disease is positively correlated with exercise capacity but not with quality of life. *Clin Res Cardiol*. 2012;101:55-61
45. Moalla W, Dupont G, Costes F, Gauthier R, Maingourd Y, Ahmaidi S. Performance and muscle oxygenation during isometric exercise and recovery in children with congenital heart diseases. *Int J Sports Med*. 2006;27:864-869
46. Brassard P, Bedard E, Jobin J, Rodes-Cabau J, Poirier P. Exercise capacity and impact of exercise training in patients after a fontan procedure: A review. *Can J Cardiol*. 2006;22:489-495
47. Fredriksen PM, Veldtman G, Hechter S, Therrien J, Chen A, Warsi MA, Freeman M, Liu P, Siu S, Thaulow E, Webb G. Aerobic capacity in adults with various congenital heart diseases. *Am J Cardiol*. 2001;87:310-314
48. Tikkanen AU, Oyaga AR, Riano OA, Alvaro EM, Rhodes J. Paediatric cardiac rehabilitation in congenital heart disease: A systematic review. *Cardiol Young*. 2012;22:241-250
49. Zipes DP, Ackerman MJ, Estes NA, 3rd, Grant AO, Myerburg RJ, Van Hare G. Task force 7: Arrhythmias. *J Am Coll Cardiol*. 2005;45:1354-1363
50. Vella CA, Robergs RA. A review of the stroke volume response to upright exercise in healthy subjects. *British journal of sports medicine*. 2005;39:190-195
51. Erbs S, Hollriegel R, Linke A, Beck EB, Adams V, Gielen S, Mobius-Winkler S, Sandri M, Krankel N, Hambrecht R, Schuler G. Exercise training in patients with advanced chronic heart failure (NYHA

IIIb) promotes restoration of peripheral vasomotor function, induction of endogenous regeneration, and improvement of left ventricular function. *Circ Heart Fail*. 2010;3:486-494

52. Ploeger HE, Takken T, de Greef MH, Timmons BW. The effects of acute and chronic exercise on inflammatory markers in children and adults with a chronic inflammatory disease: A systematic review. *Exerc Immunol Rev*. 2009;15:6-41
53. Nettle H, Sprogis E. Pediatric exercise: Truth and/or consequences. *Sports Med Arthrosc*. 2011;19: 75-80
54. Goldstein BH, Golbus JR, Sandelin AM, Warnke N, Gooding L, King KK, Donohue JE, Gurney JG, Goldberg CS, Rocchini AP, Charpie JR. Usefulness of peripheral vascular function to predict functional health status in patients with fontan circulation. *Am J Cardiol*. 2011;108:428-434



Chapter 3

Long-term outcomes of transatrial-transpulmonary repair of tetralogy of Fallot.

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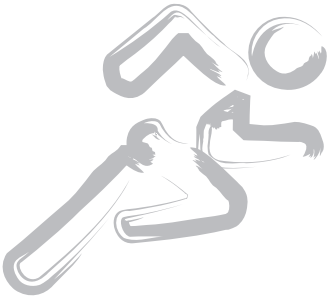


ABSTRACT

Objectives: The surgical approach to repair of tetralogy of Fallot (ToF) has shifted over the years. We aimed to report the long-term follow-up after ToF repair with the transatrial–transpulmonary approach and to determine predictors of long-term outcomes.
Methods: Retrospective analysis of patients operated on in two tertiary referral centers. Primary outcome measures were: death, pulmonary valve replacement (PVR), reintervention for other reasons, internal cardioverter-defibrillator and/or pacemaker placement. Kaplan– Meier assessment of overall and event-free survival as well as uni- and multivariate analyses of risk factors for outcomes were performed.
Results: Four hundred and fifty-three patients were included. Median age at operation was: 0.6 years (range 0 – 19.6) and median age at the last follow-up was 14.3 years (range 0.1 – 42.1). Median age at repair decreased from 1.2 years (range 0.6 – 5.8) (1970 – 80) to 0.3 years (range 0 – 4.7) (2000 – 12). A transannular patch (TP) was used in 65% of all patients. The use of a TP showed a decline from 89% in the initial years of the cohort to 64% in 2000 – 12. Early mortality was 1.1% (5 patients) for the entire cohort and late mortality 2.4% (11 patients). Overall survival for the entire cohort was 97.3% (95% CI 95.7 – 98.8) and 91.8% (95% CI 85.9 – 97.7) at 10 and 25 years, respectively. For patients with a TP (n = 294) vs non-TP (n = 159), this was 97.2% (95% CI 95.2 – 99.2) vs 97.5% (95% CI 95.1 – 99.9) at 10-year and 91.0% (95% CI 83.9 – 98.1) vs 96.3% (95% CI 93.0 – 99.6) at 25-year follow-up (P = 0.958). Fifty-two patients underwent PVR, and in 5 a pacemaker was inserted. Event-free survival for TP versus non-TP patients was 80.2% (95 CI% 75.5 – 84.9) vs 81.7% (95% CI 75.2 – 88.2) at 10-year and 27.9% (95% CI 17.7 – 38.1) vs 78.5% (95% CI 71.4 – 85.6) at 25-year follow-up (P = 0.016). In multivariate analysis, both the use of a TP (HR 1.705, 95% CI 1.023 – 2.842) and the year of surgical repair of tetralogy of Fallot (HR 1.039, 95% CI 1.006 – 1.073) were associated with a higher probability of an event.
Conclusions: ToF patients corrected with the transatrial–transpulmonary approach have good long-term survival. PVR is a frequent event at longer follow-up and other events are limited. The use of a TP is a predictor for poorer event-free outcomes, increasing the risk of the composite endpoint 1.7 times.

INTRODUCTION

Surgical correction of tetralogy of Fallot (ToF) is reported to date back as early as 1954. Since then major developments have resulted in excellent present-day survival in ToF patients, which is, however, still reduced compared to the overall population[1].

Over the years the surgical approach to ToF has shifted from a repair via a right ventriculotomy, commonly combined with a patch in the right ventricular outflow tract (RVOT), often after initial palliative shunting, to a transatrial-transpulmonary approach often as primary repair[1]. The aim of the latter approach was to minimize the unfavorable side effects associated with a ventriculotomy, such as transmural myocardial scarring and coronary artery damage, which were thought to contribute to long-term impairment of right ventricular function and the risk for ventricular arrhythmias[2].

Long-term complications like decreased exercise intolerance, (right) heart failure, arrhythmias and sudden death are well-known to occur after repair of ToF[2]. Pulmonary valve replacement (PVR) and, to a lesser extent, internal cardioverter-defibrillator (ICD) placement are common procedures long-term after repair of ToF.

Predictors for negative long-term outcome after ToF repair have been studied extensively and include the amount of residual pulmonary regurgitation (PR), right and left ventricular size and function, myocardial tissue composition, right ventricular outflow function and electrical inhomogeneity[2-6]. Despite extensive literature on the results of ToF repair, relatively limited information is available specifically on the long-term outcomes of the transatrial-transpulmonary approach. Many studies on the subject of long-term outcome of ToF repair have not focused on the outcomes of this approach, have used different criteria to define the population with ToF that was included, or have been hampered by small patient numbers or short duration of follow-up[7, 8].

The aims of this study were to report the long-term follow up after ToF repair with the transatrial-transpulmonary approach in a relatively large cohort and to determine predictors of long-term adverse outcome.

PATIENTS AND METHODS

Patients

A retrospective analysis was made of all patients that underwent ToF repair with a transatrial-transpulmonary approach in two tertiary referral centers in the Netherlands, with special attention to whether a transannular patch (TP) was used or not (non-TP). Data of all patients born after January 1st 1970 and who had undergone ToF repair were analyzed. ToF was defined as ventricular septal defect with anterior deviation of the outflow septum, without major anomalies, requiring desobstruction of right

ventricular outflow obstruction and closure of ventricular septal defect. Patients with other diagnoses including pulmonary atresia (PA), double outlet right ventricle (DORV), atrioventricular septal defect (AVSD) and absent pulmonary valve syndrome (APVS) were excluded. Other exclusion criteria were patients whose surgical reports were not available, patients with insufficient follow-up data and patients who did not have a transatrial-transpulmonary ToF repair.

In general, in all the years of the study, the transatrial-transpulmonary strategy essentially consisted of right atriotomy as first step in the approach of the VSD and the RVOT. As second step the main pulmonary artery was opened with a longitudinal incision as an approach to the pulmonary valve and the subvalvular area. Only after endoventricular desobstruction of the RVOT and when considered necessary by the attending surgeon, this incision was continued along the length of the infundibulum and reconstructed with a TP to create an adequate diameter of the RVOT. Patients in whom primarily a ventriculotomy was performed were excluded from our study.

Patients were included if treated in the Erasmus Medical Center (EMC), Rotterdam or the Radboud University Medical Center Nijmegen (RUMC), Nijmegen, the Netherlands.

The study complies with the regulations of institutional review boards with regard to retrospective data collection.

Methods

Data collection

The medical and surgical records of all patients were reviewed. Demographic characteristics are given in table 1. Characteristics of the ToF repair including operative techniques and preoperative parameters were collected (table 2). Postoperative complications were scored.

Primary outcomes were defined as death, PVR, late reoperations other than PVR, balloon dilatations for pulmonary stenosis (PS) and the placement of an ICD or pacemaker. Patient status was checked in the municipal basic administration (GBA) in the Netherlands. Patients lost to follow-up were censored at the last known follow-up date according to hospital records and / or the municipal basic administration. We recorded and analyzed the last outpatient visits for all patients in the period from 1 January 2010 until 30 June 2012. Collected parameters were: length, weight, use of medication, QRS-duration and QTc-time (corrected QT-time) on ECG, severity of PR, PS and RV dilatation on echocardiography and VO_2 max, maximal work load and maximal heart rate at graded step-wise bicycle cardiopulmonary exercise testing. The presence of residual PS was recorded if a mean echocardiographic gradient of ≥16 mmHg was present. The severity of pulmonary and tricuspid regurgitation (TR) was assessed semi-quantitatively on echocardiography[9]. MRI data obtained in relation to the latest outpatient visit were recorded. MRI volumetric data was indexed to body surface area.

Table 1: Patient characteristics, demographic

	Number of patients (n = 453) (%)
Male (%)	286 (63.1)
Mean duration of pregnancy (weeks)	(n = 290) 38.54 ± 2.70
Mean birth weight (kg)	(n = 266) 2.98 ± 0.75
Median time to diagnosis (days)	(n = 333) 36.00 (0 - 3504)
Other cardiac anomalies (%)	436 (96.2)
ASD (%)	359 (82.3)
PDA (%)	89 (20.4)
Unicuspid pulmonary valve (%)	29 (6.7)
Bicuspid pulmonary valve (%)	228 (52.3)
Right aortic arch (%)	70 (16.1)
Aberrant coronary origin (%)	22 (5.0)
Previous palliative shunts (%)	58 (12.8)
Mean PS gradient before repair (mmHg)	(n = 224) 74 ± 25

Data are either mean ±SD or median with range. PS: pulmonary stenosis; PDA: patent ductus arteriosus, ASD: atrial septal defect.

Complications after ToF repair were defined as infection, arrhythmia, early reoperation (within 30 days of complete repair), fluid retention and prolonged use of inotropic drugs (>48hr).

Table 2: Characteristics of TOF repair

	All Patients	TOFr between 1970-1980	TOFr between 1980-1990[1]	TOFr between 1990-2000[2]	TOFr between 2000-2012[3]	P-value[1-2]	P-value[2-3]
Number of patients	453	9	72	165	207		
Median age at repair (years)	0.58 (0.19 - 58)	1.17 (0.58 - 5.75)	1.58 (0.08 - 9.75)	0.75 (0 - 19.58)	0.33 (0 - 4.67)	<0.001	<0.001
Transpulmonary approach (%)	429 (94.7)	9 (100.0)	72 (100.0)	158 (95.8)	190 (91.8)	0.105	0.122
Valvulotomy (%)	177 / 450 (39.3)	0 (0.0)	23 (31.9)	80 (48.5)	74 (36.3)	0.018	0.018
Transannular patch (%)	294 (64.9)	8 (88.9)	56 (77.8)	98 (59.4)	132 (63.8)	0.006	0.388
Reoperation within 30 days of TOFr	20 (4.4)	1 (11.1)	9 (12.5)	6 (3.6)	4 (1.9)	0.017	0.349

Either mean ± SD or median with range for numerical variables was used. ToFr: surgical repair of tetralogy of Fallot. [1-2]p-value for comparison of the groups between 1980-1990 and 1990-2000. [2-3]p-value for comparison of the groups between 1990-2000 and 2000-2012.

Data analysis

Statistical analyses were performed with IBM SPSS Statistics 20 (SPSS, Inc., USA). We tested with a significance level of 0.05.

Data were summarized for all patients using frequencies and percentages for categorical variables and either mean ± standard deviation (SD) or median with range for numerical variables.

A student's t-test was used to compare means between independent groups. In case a value did not have a normal distribution, we calculated the medians and used a (non-parametric) Mann-Whitney test to compare these medians between the groups. We used a χ^2 test to compare categorical variables with a normal distribution between independent subgroups. When a categorical value was not distributed normally, Fisher exact test was used to compare these variables between groups. Chi-squared approximation was not considered suitable when the expected values in any of the cells of a table are below 5.

The probability of long-term survival and event-free survival was estimated by Kaplan-Meier curves. A log-rank test was used to compare these curves between different groups.

With a Cox proportional hazard analysis (forward step-wise regression method) we analyzed whether parameters had an influence on the probability of an event. The seven best parameters in univariate analysis were included in the multivariate analysis. We composed a composite endpoint, which was defined as death, PVR, other (late: after 30 days after complete repair) reoperations, balloon dilatations for PS or pacemaker insertion.

RESULTS

Patient characteristics

We identified 465 patients who met the inclusion criteria, as shown in figure 1; 288 patients from Center 1 and 165 patients from Center 2 were included. Twelve patients were excluded because they were lost to follow-up. Eleven patients had their ToF repair in the Netherlands but lived abroad and were lost to follow-up. In 1 patient, the follow-up was insufficient.

Table 1 summarizes patient characteristics of the 453 patients; 63.1 % was male. In 96.2% of the patients associated cardiac anomalies were found: secundum type atrial septal defect in 82.3 %, patent ductus arteriosus in 20.4%, uni- and bicuspid pulmonary valve in respectively 6.7% and 52.3%. A coronary artery had an aberrant origin in 5% of the patients and 16.1% had a right aortic arch.

Prior to TOF repair 12.8% of the patients received a palliative shunt, as shown in table 1. This percentage was significantly higher in the patients who later received a TP

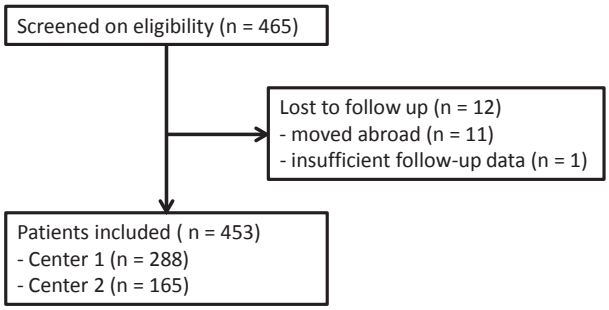


Figure 1: Flow-chart of patient enrollment
ToF: tetralogy of Fallot.

compared with those who did not (15 % (n = 45) versus 8 % (n = 13) ($p = 0.030$). Mean PS gradient before complete repair was higher in the TP group compared to the non-TP group (80 ± 24 (n = 134) vs 66 ± 25 (n = 90) mm Hg ($p < 0.001$). The median age at repair of ToF was 0.6 (0 - 19.6) years, as shown in table 2. Of the 453 patients, a TP was used in 215 (47.5%) patients, and both a TP and valvotomy were done in 79 (17.4%). In further analysis these 294 patients were termed the TP group. In 98 (21.6%) patients, only pulmonary valvotomy was performed, and in 61 (13.5%) patients no valvotomy and no TP were required. These patients were included as the not-TP group (n = 159).

A total of 20 patients received an early reoperation within 30 days of ToF repair, as shown in table 2. Eleven patients needed rethoracotomy due to rebleeding, 7 due to a residual VSD and 2 because of residual RVOT obstruction.

A trend towards decreasing median age at ToF repair over time was noted: in the cohort 1970 - 1980 median age at repair was 1.8 (0.6 - 5.8) years, compared with 0.3 (0 - 4.7) years in the cohort 2000 - 12. Valvulotomy increased during the years from 0.0% in the cohort 1970 - 1980 to 48.5% in the cohort 1990 - 2000, with a slight decrease in the cohort 2000 - 12 to 36.3%. The use of a TP shows a reverse trend: it decreased from 88.9% in the first cohort to 59.4% in the cohort 1990 - 2000, with a slight increase in the last cohort to 63.8%.

A total of 77 patients (17.0%) were diagnosed with a genetic syndrome or association. In 28 patients this concerned trisomy 21, in 25 patients 22q11 deletion, in 7 patients vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula and/or esophageal atresia, renal & radial anomalies and limb defects (VACTERL) association and in 17 patients a range of individual gene abnormalities, syndromes or associations.

Survival and event-free survival

Sixteen patients died during follow up. This represents 3.5% of the study population. Early mortality (within 30 days of ToF repair) was 1.1% (5 patients); late mortality was 2.4% (11 patients). The median age at time of death was 1.8 (0.1 - 32.8) years. Eight patients died

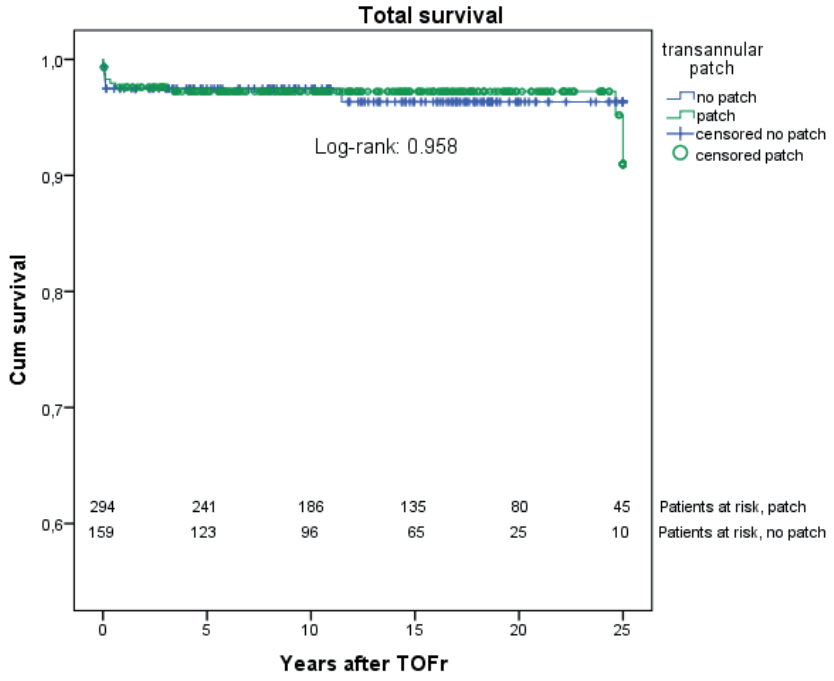


Figure 2: Kaplan Meyer curve for overall survival

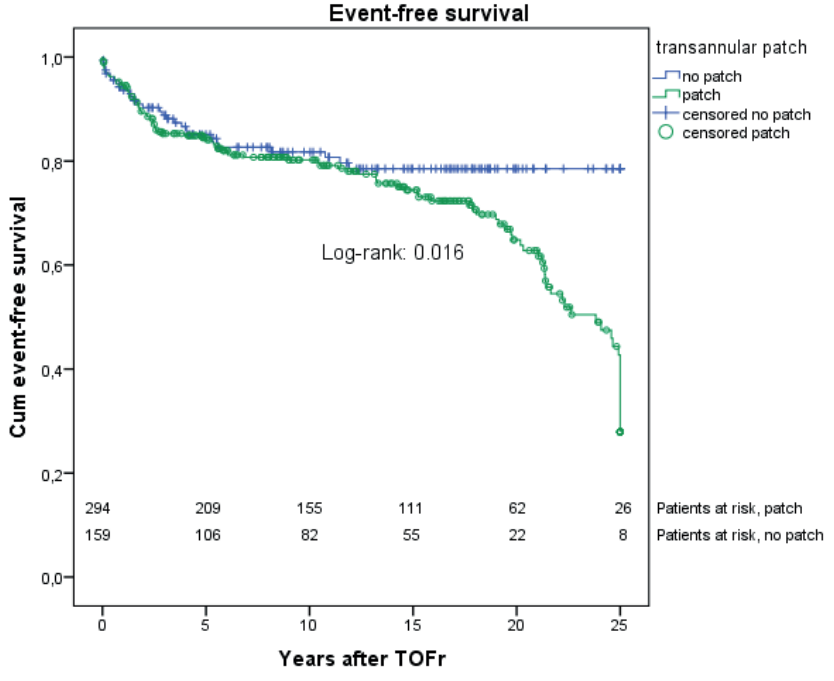


Figure 3: Kaplan-Meyer curve for event-free survival

from cardiac causes, 6 from non-cardiac causes and in 2 patients the cause of death was unknown. Down-syndrome was diagnosed in 3 of the deceased patients, 2 deceased patients had the VACTERL-association.

The cumulative overall survival was 97.3% (95% CI 95.7 - 98.8) at 10 years and 91.8% (95% CI 85.9 - 97.7) at 25 years after ToF repair. Figure 2 shows the cumulative overall survival for patients with and those without a TP. Survival for the TP group was 97.2%(95% CI 95.2 - 99.2) at 10 years and 91.0% (95% CI 83.9 - 98.1) at 25 years after ToF repair, compared with 97.5% (95% CI 95.1-99.9) at 10 years and 96.3% (95% CI 93.0-99.6) at 25 years in the non-TP group ($p = 0.958$).

The cumulative overall event-free survival was 80.7% (95% CI 76.9 - 84.6) at 10 years and 37.0% (95% CI 27.2 - 46.8) at 25 years after ToF repair. In figure 3 the event-free survival is shown for the patients with and those without a TP. For the TP-group the cumulative total event-free survival is 80.2% (95% CI 75.5 - 84.9) at 10 years and 27.6% (95% CI 17.7 - 38.1) at 25 years; for the non-TP group it is 81.7% (95% CI: 75.2 - 88.2) at 10 years and 78.5% (95% CI 71.4 - 85.6) at 25 years after ToF repair. The differences in event-free survival were statistically significantly different ($p = 0.016$).

Long-term outcomes

In table 3, the long-term outcomes of all patients are shown. The patients are divided into two groups: TP (n = 294) and non-TP (n = 159). The median age at the end of the follow-up period for the entire cohort is 14.4 (0.1 – 42.1) years. There was no significant difference between the median age at the end of follow-up between the two subgroups. A total of 52 patients underwent a first PVR; this was 11.5% of the study population. The first PVR was performed at a median of 20.2 (1.9 – 34.8) years after the ToF repair. In the TP group, 51 (17.3%) patients received a PVR, and in the non-TP group only 1 patient (0.6%) did ($p < 0.001$). As shown in Table 3, a total of 72 (15.9%) patients needed a late reoperation other than PVR, 17.0% in the TP group and 13.8% in the non-TP group ($p =$ not significant). Reoperations performed were infundibulectomy (desobstruction of the RVOT) combined with reconstruction of the pulmonary artery in 3.3% of all patients. Isolated infundibulectomy (RVOT desobstruction) was performed in 4.9% of all patients and isolated reconstruction of the pulmonary was performed in 1.8% of all patients.

Clinical state at latest evaluation

In table 4, information regarding the last outpatient visit between 2010 and 2012 is given. Three hundred and sixty patients were seen in that setting in this period, 49 of whom had had a PVR.

Patients in the PVR group were significantly older than those in the non-PVR group: 27.7 (10.9 – 42.1) compared with 11.7 (0.3 – 36.1) years ($p < 0.001$). The median age at follow-up post-ToF repair was also significantly higher in the PVR group.

Table 3: Outcomes all patients with or without a transannular patch

	Patients (n = 453)	Transannular patch (n = 294)	No transannular patch (n = 159)	*p*-value
Median age at end follow-up (years)	14.35 (0.09 - 42.13)	14.73 (0.09 - 42.13)	13.69 (0.24 - 35.05)	0.451
Median time after TOFr (years)	13.31 (0.00 - 36.31)	14.06 (0.00 - 36.31)	12.59 (0.00 - 33.87)	0.342
Patients with follow up >15 years	200	135	65	
Patients with follow up >20 years	105	80	25	
Patients with follow up >25 years	55	45	10	
1st PVR (%)	52 (11.5)	51 (17.3)	1 (0.6)	<0.001
Median follow-up after repair (years)	20.18 (1.93 - 34.78)	20.25 (1.93 - 34.78)	14.45	-
1st PVR (%)	52 (11.5)	51 (17.3)	1 (0.6)	<0.001
Median follow-up after repair (years)	20.18 (1.93 - 34.78)	20.25 (1.93 - 34.78)	14.45	-
2nd PVR (%)	3 (0.7)	3 (1.0)	0 (0.0)	0.555
Pacemaker (%)	5 (1.1)	5 (1.7)	0 (0.0)	0.167
Balloon dilatation for PS	32 (7.1)	24 (8.2)	8 (5.0)	0.214
Median follow up after repair (years)	2.64 (0.39 - 27.37)	2.52 (0.79 - 27.37)	3.11 (0.39 - 8.16)	0.683
Re-operations other than PVR	72 (15.9)	50 (17.0)	22 (13.8)	0.378
Median follow up after repair (years)	1.42 (0 - 18.87)	1.20 (0 - 18.87)	2.42 (0 - 11.92)	0.443
Infundibulectomy and reconstruction pulmonary artery	15 (3.3)	7 (2.4)	8 (5.0)	0.132
Infundibulectomy	22 (4.9)	15 (5.1)	7 (4.4)	0.741
Reconstruction pulmonary artery	8 (1.8)	5 (1.7)	3 (1.9)	-
Death during follow-up (%)	16 (3.5)	11 (3.7)	5 (3.1)	0.937
Median age at time of death (months)	20.50 (1 - 394)	25.00 (1 - 394)	5.00 (2 - 152)	-

We used either mean ±SD or median with range for numerical variables. PVR: pulmonary valve replacement; ToFr: surgical repair of tetralogy of Fallot.

Table 4: Clinical state at latest evaluation

	Patients (n = 360)	Non PVR group (n = 311)	PVR-group (n = 49)	P-value
Median age (years)	13.68 (0.27 - 42.13)	11.70 (0.27 - 36.14)	27.77 (10.86 - 42.13)	<0.001
Adults (%)	106 (29.4)	65 (20.9)	41 (83.7)	<0.001
Mean BMI adults	(n = 80) 23.28 ± 4.20	(n = 52) 23.43 ± 4.47	(n = 28) 23.00 ± 3.73	0.668
BMI >25 (%)	21 (26.2)	14 (26.9)	7 (25.0)	0.852
Current use of medication (%)	11 / 339 (3.2)	5 / 295 (1.7)	6 / 44 (13.6)	0.001
Median follow up age post correction (years)	12.00 (0 - 35)	10.00 (0 - 33)	24.00 (9 - 35)	<0.001
post 1st PVR (years)			3.00 (0 - 19)	
Electrocardiography data (n)	341	295	46	
Mean QRS duration (msec)	(n = 324) 121.08 ± 25.85	(n = 278) 118.56 ± 25.07	(n = 46) 136.28 ± 25.49	<0.001
QRS >180 msec (%)	5 (1.5)	3 (1.1)	2 (4.3)	0.149
Mean QTc time (msec)	(n = 275) 425.46 ± 34.18	(n = 229) 426.86 ± 35.01	(n = 46) 418.52 ± 29.08	0.132
Echocardiographic data (n)	298	261	37	
PR (n)	276	242	34	
No PR (%)	10 (3.6)	7 (2.9)	3 (8.8)	0.112
Mild PR (%)	74 (26.8)	52 (21.5)	22 (64.7)	<0.001
Moderate PR (%)	120 (43.5)	111 (45.9)	9 (26.5)	0.033*
Severe PR (%)	72 (26.1)	72 (29.8)	0 (0.0)	<0.001
RV dilatation (n)	216	189	27	
No RV dilatation (%)	37 (17.1)	34 (18.0)	3 (11.1)	0.584
Mild RV dilatation (%)	70 (32.4)	61 (32.3)	9 (33.3)	0.912
Moderate RV dilatation (%)	104 (48.1)	89 (47.1)	15 (55.6)	0.410
Severe RV dilatation (%)	5 (2.3)	5 (2.6)	0 (0.0)	-

Table 4 (continued)

	Patients (n = 360)	Non PVR group (n = 311)	PVR-group (n = 49)	P-value
Tricuspid regurgitation	193 / 246 (78.5)	161 / 210 (76.7)	32 / 36 (88.9)	0.099
PS ≥ 16mmHg	129 / 184 (70.1)	102 / 154 (66.2)	27 / 30 (90.0)	0.009
Ergometry (n)	58	47	11	
Mean % of predicted max VO2	(n = 34) 87.82 ± 17.61	(n = 28) 89.43 ± 17.98	(n = 6) 80.33 ± 14.84	0.257
Mean % of predicted max watt	(n = 50) 88.56 ± 16.25	(n = 40) 88.88 ± 16.54	(n = 10) 87.30 ± 15.80	0.787
Mean max HF	(n = 51) 174.45 ± 17.32	(n = 41) 175.61 ± 17.04	(n = 10) 169.70 ± 18.54	0.338
MRI (n)	49	42	7	
Mean LV EDV (ml/m2)	82.98 ± 14.18	82.54 ± 13.31	85.43 ± 19.43	0.625
ESV (ml/m2)	36.07 ± 11.16	35.28 ± 11.38	40.43 ± 9.40	0.266
SV (ml/m2)	47.52 ± 9.04	47.97 ± 8.60	45.00 ± 11.66	0.429
EF (%)	57.47 ± 7.96	58.26 ± 8.21	52.71 ± 3.86	0.088
Mean RV EDV (ml/m2)	131.04 ± 37.04	131.82 ± 35.11	126.71 ± 49.56	0.741
ESV (ml/m2)	68.57 ± 26.57	67.28 ± 24.26	75.71 ± 38.69	0.446
SV (ml/m2)	62.72 ± 17.33	64.82 ± 17.48	51.00 ± 11.42	0.051
EF (%)	49.45 ± 8.13	50.67 ± 7.71	42.14 ± 7.06	0.009
PI (%)	32.73 ± 16.95	33.00 ± 14.59	(n = 3) 29.33 ± 42.34	0.895

We used either mean ±SD or median with range for numerical variables. BMI: body mass index, PVR: pulmonary valve replacement, PR: pulmonary regurgitation; RV: right ventricle; PS: pulmonary stenosis; VO2: maximal oxygen consumption; HF: heart frequency; QTc: corrected QT-time; LV EDV: left ventricle end-diastolic volume; ESV: end-systolic volume; SV: stroke volume; RV EDV: right ventricular end-diastolic volume; PI: pulmonary insufficiency.

Electrocardiography was performed in 341 patients and QRS duration was assessed in 324 patients. A significant difference ($P < 0.001$) was found in mean QRS duration between the two groups. In the PVR group, the mean QRS duration was 136 ± 25 ms, compared with 119 ± 25 ms in the non-PVR group. The mean QRS duration in all patients was 121 ± 26 after a mean follow-up of 12 years, and 5 patients had QRS duration of more than 180 ms.

In 298 patients, an echocardiogram was performed. Seventeen percent of patients had no RV dilatation; mild dilatation was found in 32% of patients, moderate dilatation in 48% and severe dilatation in 2%. Echocardiography did not show statistically significant differences for RV size between the TP and non-TP groups.

A more than minimal residual PS gradient was found in 70% of the patients. Patients in the PVR group had significantly more PS than those in the non-PVR group: 90.0% compared with 66.2% ($p = 0.009$).

In 246 patients, TR was noted at echocardiography. No TR was found in 21.5% of the patients, mild TR in 67.4% and moderate TR in 10.6%. In 0.4% of the patients, severe TR was found. Two patients with moderate TR underwent a PVR. and the patient with severe TR had a pacemaker due to a third-degree heart block.

Predictors for negative outcome

Table 5 presents the results of Cox proportional hazard analysis of the most important parameters for the combined event. Univariate analysis showed that the use of a TP during ToF repair was associated with a higher probability of an event (HR 1.631, 95% CI 1.077 – 2.471). Also, postoperative complications after ToF repair (HR 1.506, 95% CI 1.035 – 2.191), year of TOFr (HR 1.034, 95% CI 1.007 – 1.061) and age at TOFr (HR 0.987, 95% CI 0.976 – 0.997) were associated with a higher risk. The parameters Hb level before ToF repair, male gender and the presence of a genetic disorder did not show a significant association in univariate analysis.

Table 5: Cox-regression combined event

	Univariate		Multivariate	
	HR	95% CI	HR	95% CI
Transannular patch	1.631*	1.077 - 2.471	1.705*	1.023-2.842
Complications after TOFr	1.506*	1.035 - 2.191	-	-
Year of TOFr	1.034*	1.007 - 1.061	1.039*	1.006-1.073
Hb level before TOFr	1.013	0.930 - 1.103	-	-
Age at TOFr (months)	0.987*	0.976 - 0.997	-	-
Gender	0.873	0.611 - 1.247	-	-
Genetic disorder	0.800	0.480 - 1.334	-	-

*Statistically significant factor with P-value < 0.05.

In multivariate analysis, both the use of a TP (HR 1.705, 95% CI 1.023 – 2.842) and year of TOFr (HR 1.039, 95% CI 1.006 – 1.073) were associated with a higher probability of an event.

In hazard analysis for the event death, both uni- and multivariate analyses did not show significant associations.

DISCUSSION

This study shows that overall, ToF patients corrected with the transatrial–transpulmonary approach have excellent survival rates. Over several decades, the operative mortality (5 of 453 patients) was 1.1%, and 25-year overall survival rate was 92%, more specifically 91% in the TP group and 96% in the non-TP group. In the time-span we studied, there was a clear trend towards repair at younger age and a decrease in the use of transannular patching of the RVOT, confirming other reports on this subject.

Whereas 10- to 15-year survival has been documented frequently in various cohorts of ToF, relatively few studies have reported on 25-year survival after ToF repair. In 2008, a group from Toronto reported a 25-year survival of ~90% for ToF without PA, DORV, AVSD or branch PS, in patients born before 1984[10]. Recently, 25-year overall survival in a large Korean cohort was reported to be 93%, with statistically better survival for transatrial and non-transannular approaches[11]. The improvements in survival, in part, relate to improved early mortality[10]. While long-term deterioration of clinical state and the need for reinterventions are commonly recognized, it is less clear whether the mortality risk increases with time[10]. Considering the low rate of late mortality in our patients, this could not be assessed from our data. Of note, only 3.5% of the patients died, many of whom had associated genetic abnormalities. Most of these patients were relatively young at time of death. The number of patients who died late in follow-up in our cohort is very low. The explanation probably lies in the fact that with the surgical approach as described, these patients are in good clinical condition after ToF repair and apparently have a good prognosis with regard to survival for the observed period[6, 12].

Timely reintervention is another factor to consider. In fact, there is a clear increase of reinterventions with time, particularly after 15-year follow-up. There was a clear difference in event-free survival for the TP versus the non-TP group. Multivariate analysis demonstrated that the use of a TP in the setting of transatrial– transpulmonary approach was associated with a 1.7 times higher risk of the composite endpoint of death, PVR, reoperation for other reasons, balloon dilatation for PS or pacemaker placement in our patients. This confirms findings from earlier reports in combined cohorts[2]. Since the use of a TP depends on the anatomy and hemodynamics at initial repair and often cannot be avoided, this emphasizes the importance of comparison of results among clearly defined and highly comparable populations[5, 10, 13].

Event-free survival differs significantly from overall survival in most series. The majority of reinterventions is related to the long-term effects of PR and particularly consists of PVR. At a median follow-up of 15 years, 17% of our patients who had transannular patching of their RVOT at the initial repair had PVR; this compares favorably with similar reports in the literature[10, 11].

Patients without a TP had better event-free survival. These types of observations resulted in attempts to avoid transannular patching and avoid damage[1-24] to the pulmonary valve and/or infundibulum[1, 8].

Recently, Bove et al.[8] demonstrated in an experimental setting that of the available alternatives, extensive transannular patching results in the most severely dilated and functionally impaired right ventricles. Whether the alternative TP-avoiding strategies will result in improved (event-free) survival of patients is to be seen; in earlier studies, this could not be demonstrated[5, 8]. The trade-off of restrictive strategies aimed to avoid residual PR may be an increased reoperation rate for residual stenosis. Preliminary data from a large registry study may point towards an increased risk of arrhythmias and sudden death in patients with residual RV outflow obstruction and RV hypertrophy[17].

The long-term problems related to chronic PR are well known and include right ventricular dilatation, impaired right and left ventricular function and increased risk of arrhythmias. Risk factors for late problems related to PR have been identified and include the amount of residual PR, right and left ventricular size and function, myocardial tissue composition, right ventricular infundibular and outflow tract function, right atrial function and electrical inhomogeneity[2-5, 22]. Many of these risk factors cannot be fully avoided, despite individualized operative strategies aimed at preservation of RVOT function.

A remarkable finding of our study is the lack of improvement in exercise performance, pro-arrhythmic ECG parameters, ventricular size and an increase in RVOT stenosis in patients after PVR. Although this data must be interpreted with caution considering the limited number of observations for some parameters, this questions the timing and effects of PVR. Considerable debate exists with regard to indications for PVR. Current guidelines include factors from history, ECG signs of increased electrical inhomogeneity and hemodynamic factors related to residual RVOT problems[17]. These factors include older age at repair and ECG parameters, particularly QRS duration. Recommendations with regard to RV size provide a wide range of end-diastolic dimensions, from ±140 to ±180 ml/m2 body surface area[15, 16]. In this size range of the RV, normalization of systolic RV function after restoration of pulmonary valve competency and resection of the dilated RV outflow has been demonstrated. Whether this results in improved long-term survival has not yet been established[18].

Recent data suggest that patients with intermediate RV dilatation (132 ± 9 ml/m2) and severe PR (40 ± 3%) are at low risk of significant progression of RV size in the short

term, suggesting that some delay in PVR may be acceptable in this group[23]. PVR may also induce some degree of RVOT stenosis, as was noted in our patient group. This could be caused by the use of a relatively small homograft or by deterioration of the homograft[24].

The lack of change in important pro-arrhythmic parameters, such as QRS duration and QTc time, reflects earlier observations[18]. In a study that has been criticized for problems related to adequate matching of the groups involved, Harrild et al.[18] could not demonstrate a beneficial effect of PVR with regard to post-PVR occurrence of ventricular tachycardia or death. The implications of these observations are that current long-term treatment strategies may require modification[17].

A common indication for reintervention after ToF repair is prevention or treatment of hemodynamically important arrhythmias. The burden of arrhythmias is considerable in these patients, particularly in the adult age range. Atrial arrhythmias occur frequently, in up to one-third of the patients[20]. Pacemaker implantation, for bradycardia and tachycardia/bradycardia syndromes, is required in up to 8%[20]. Hemodynamic factors and prior surgeries are among the most important risk factors. In our population, pacemaker implantation was relatively infrequent and was required only in the TP group[3, 6].

More than moderate TR may be another indication for reintervention. The occurrence of more than minimal TR in our series was limited and comparable/compares favorably with other recent reports. Important TR may relate to intrinsic valve abnormalities, traction on the tricuspid annulus or damage to tricuspid structures during repair or to RV dilatation in the setting of impaired RV function[19]. In recent series, late TR did not differ between transatrial and transventricular approaches to ToF repair.

Since the 1970s, less than 10% of ToF repairs in our institutions have been performed with the transventricular approach, which has hampered a direct comparison between results of transatrial and transventricular repairs. Recent single- and multicenter data suggest that both techniques can be used successfully.

Ventriculotomy has been thought to contribute to long-term impairment of right ventricular function and the risk of ventricular arrhythmias. Whether the transatrial–transpulmonary approach has actually resulted in long-term benefits for the patients is still a subject of debate. The transatrial–transpulmonary approach does not use a ventriculotomy in the body of the RV and a limited, if any, incision of the RV outflow tract. Comparison of results is often difficult, since different approaches in time, different anatomical variants and different age groups have been included in different studies. Furthermore, the long-term effects of the approach to VSD closure and of RV outflow desobstruction are hard to distinguish. Lindberg et al.[5] in a single-center study of 570 patients did not find any difference in long-term outcomes of transatrial versus transventricular repair. Any transannular incision increased the risk of reinterventions, but did not impact on long-time survival[5, 11]. In the series of Alexiou et al.[14] a significantly higher reintervention rate at 10- and 20-year follow-up was noted in the atrial versus

the transventricular approach, particularly for RV outflow obstruction, for reasons that were not clear to the authors. This has not been a common observation[5, 6]. Data from the Society of Thoracic Surgeons Database and of the European Association for Cardio-Thoracic Surgery Congenital Database have shown that both approaches continue to be used widely, with excellent early results and ventriculotomy and TP as the most prevalent type of operation[3, 4]. A temporal trend towards the transatrial approach has been reported in the most recent studies[3, 21].

Study limitations

A limitation of this study is the retrospective design, resulting in a considerable number of missing values. Another limitation was the small number of patients with an event. Furthermore, a direct comparison of different surgical approaches could not be made.

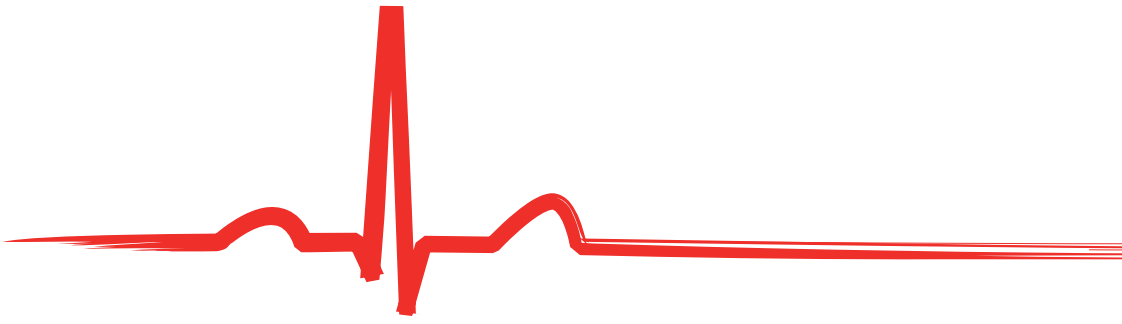
Conclusions

ToF patients corrected with the transatrial–transpulmonary approach have good long-term survival. Clinical condition after ToF repair is good; PVR is a frequent event at longer follow-up, other events are limited in number. The use of a TP at ToF repair is a predictor for poorer event-free outcome; it almost doubles the risk of the composite endpoint of death, reoperation, balloon dilatation, pacemaker placement or PVR.

REFERENCES

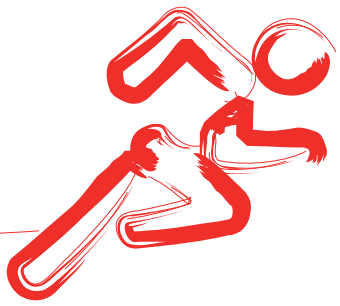
1. Boni L, Garcia E, Galletti L, Perez A, Herrera D, Ramos V, Marianeschi SM, Comas JV. Current strategies in tetralogy of fallot repair: Pulmonary valve sparing and evolution of right ventricle/left ventricle pressures ratio. *Eur J Cardiothorac Surg*. 2009;35:885-889
2. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD, Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of fallot: A multicentre study. *Lancet*. 2000;356:975-981
3. Al Habib HF, Jacobs JP, Mavroudis C, Tchervenkov CI, O'Brien SM, Mohammadi S, Jacobs ML. Contemporary patterns of management of tetralogy of fallot: Data from the society of thoracic surgeons database. *Ann Thorac Surg*. 2010;90:813-819
4. Sarris GE, Comas JV, Tobota Z, Maruszewski B. Results of reparative surgery for tetralogy of fallot: Data from the european association for cardio-thoracic surgery congenital database. *Eur J Cardiothorac Surg*. 2012;42:766-774
5. Lindberg HL, Saatvedt K, Seem E, Hoel T, Birkeland S. Single-center 50 years' experience with surgical management of tetralogy of fallot. *Eur J Cardiothorac Surg*. 2011;40:538-542
6. d'Udekem Y, Ovaert C, Grandjean F, Gerin V, Cailteux M, Shango-Lody P, Vliers A, Sluysmans T, Robert A, Rubay J. Tetralogy of fallot: Transannular and right ventricular patching equally affect late functional status. *Circulation*. 2000;102:III116-122
7. Airan B, Choudhary SK, Kumar HV, Talwar S, Dhareshwar J, Juneja R, Kothari SS, Saxena A, Venugopal P. Total transatrial correction of tetralogy of fallot: No outflow patch technique. *Ann Thorac Surg*. 2006;82:1316-1321
8. Bove T, Francois K, Van De Kerckhove K, Panzer J, De Groote K, De Wolf D, Van Nooten G. Assessment of a right-ventricular infundibulum-sparing approach in transatrial-transpulmonary repair of tetralogy of fallot. *Eur J Cardiothorac Surg*. 2012;41:126-133
9. Grothoff M, Spors B, Abdul-Khaliq H, Gutberlet M. Evaluation of postoperative pulmonary regurgitation after surgical repair of tetralogy of fallot: Comparison between doppler echocardiography and mr velocity mapping. *Pediatr Radiol*. 2008;38:186-191
10. Hickey EJ, Veldtman G, Bradley TJ, Gengsakul A, Manlhiot C, Williams WG, Webb GD, McCrindle BW. Late risk of outcomes for adults with repaired tetralogy of fallot from an inception cohort spanning four decades. *Eur J Cardiothorac Surg*. 2009;35:156-164
11. Park CS, Lee JR, Lim HG, Kim WH, Kim YJ. The long-term result of total repair for tetralogy of fallot. *Eur J Cardiothorac Surg*. 2010;38:311-317
12. van den Berg J, Hop WC, Strengers JL, de Jongste JC, van Osch-Gevers L, Meijboom FJ, Pattynama PM, Bogers AJ, Helbing WA. Clinical condition at mid-to-late follow-up after transatrial-transpulmonary repair of tetralogy of fallot. *J Thorac Cardiovasc Surg*. 2007;133:470-477
13. Pretre R. The congenital database and the streif in kitzbuhel. *Eur J Cardiothorac Surg*. 2012;42: 763-765
14. Alexiou C, Chen Q, Galogavrou M, Gnanapragasam J, Salmon AP, Keeton BR, Haw MP, Monro JL. Repair of tetralogy of fallot in infancy with a transventricular or a transatrial approach. *Eur J Cardiothorac Surg*. 2002;22:174-183
15. Buechel ER, Dave HH, Kellenberger CJ, Dodge-Khatami A, Pretre R, Berger F, Bauersfeld U. Remodelling of the right ventricle after early pulmonary valve replacement in children with repaired tetralogy of fallot: Assessment by cardiovascular magnetic resonance. *Eur Heart J*. 2005;26:2721-2727

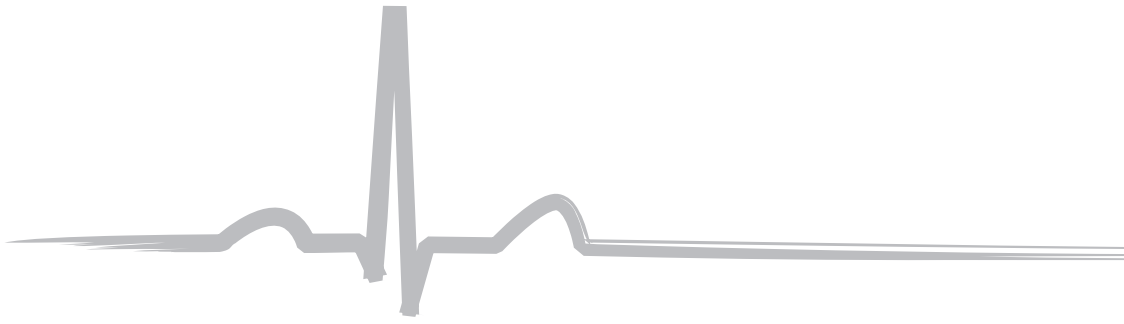
16. Frigiola A, Tsang V, Bull C, Coats L, Khambadkone S, Derrick G, Mist B, Walker F, van Doorn C, Bonhoeffer P, Taylor AM. Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: Is age a predictor of outcome? *Circulation*. 2008;118:S182-190
17. Geva T. Tetralogy of fallot repair: Ready for a new paradigm. *J Thorac Cardiovasc Surg*. 2012;143: 1305-1306
18. Harrild DM, Berul CI, Cecchin F, Geva T, Gauvreau K, Pigula F, Walsh EP. Pulmonary valve replacement in tetralogy of fallot: Impact on survival and ventricular tachycardia. *Circulation*. 2009;119: 445-451
19. Jonas RA. Early primary repair of tetralogy of fallot. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2009:39-47
20. Khairy P, Aboulhosn J, Gurvitz MZ, Opotowsky AR, Mongeon FP, Kay J, Valente AM, Earing MG, Lui G, Gersony DR, Cook S, Ting JG, Nickolaus MJ, Webb G, Landzberg MJ, Broberg CS, Alliance for Adult Research in Congenital C. Arrhythmia burden in adults with surgically repaired tetralogy of fallot: A multi-institutional study. *Circulation*. 2010;122:868-875
21. Kirsch RE, Glatz AC, Gaynor JW, Nicolson SC, Spray TL, Wernovsky G, Bird GL. Results of elective repair at 6 months or younger in 277 patients with tetralogy of fallot: A 14-year experience at a single center. *J Thorac Cardiovasc Surg*. 2014;147:713-717
22. Luijnenburg SE, Peters RE, van der Geest RJ, Moelker A, Roos-Hesselink JW, de Rijke YB, Mulder BJ, Vliegen HW, Helbing WA. Abnormal right atrial and right ventricular diastolic function relate to impaired clinical condition in patients operated for tetralogy of fallot. *Int J Cardiol*. 2013;167: 833-839
23. Quail MA, Frigiola A, Giardini A, Muthurangu V, Hughes M, Lurz P, Khambadkone S, Deanfield JE, Tsang V, Taylor AM. Impact of pulmonary valve replacement in tetralogy of fallot with pulmonary regurgitation: A comparison of intervention and nonintervention. *Ann Thorac Surg*. 2012;94:1619-1626
24. van de Woestijne PC, Mokhles MM, de Jong PL, Witsenburg M, Takkenberg JJ, Bogers AJ. Right ventricular outflow tract reconstruction with an allograft conduit in patients after tetralogy of fallot correction: Long-term follow-up. *Ann Thorac Surg*. 2011;92:161-166



Part 2

TOFFIT: a randomized controlled trial





Chapter 4

Does exercise training improve cardio-respiratory fitness and daily physical activity in children and young adults with corrected tetralogy of Fallot or Fontan circulation? A randomized controlled trial.

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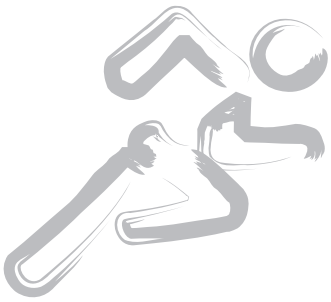


ABSTRACT

Background: Many patients with congenital heart disease do not meet current public-health guidelines to participate in moderate-to-vigorous physical activity for at least 60 minutes per day. They are less fit than their healthy peers. We hypothesized that exercise training would increase cardio-pulmonary fitness and daily physical activity in these patients. We therefore assessed effects of an exercise training program on cardio-pulmonary fitness and daily physical activity in patients with corrected tetralogy of Fallot (ToF) or Fontan circulation.

Methods: In a multi-center prospective controlled trial patients with ToF or Fontan circulation (age 10 - 25 years) were randomized, 56 patients to the exercise-group and 37 to the control-group. The exercise-group participated in a 12 week standardized aerobic exercise training program. The control-group continued lifestyle as usual. Cardiopulmonary exercise testing and activity measurements were performed before and after 12 weeks.

Results: PeakVO_2 increased in the exercise-group by 5.0% (1.7 ± 4.2 ml/kg/min, $p = 0.011$) but not in the control-group (0.9 ± 5.2 ml/kg/min, p = not significant). Workload increased significantly in the exercise-group compared to the control-group (6.9 ± 11.8 Watt vs. 0.8 ± 13.9 Watt; $p = 0.047$). Subgroup analysis showed a significant increase in pre-to-post peakVO_2 in the exercise-group of ToF patients, but not in the exercise-group of Fontan patients.

Percentage of measured time spent in moderate-to-vigorous activity at baseline was 13.6 ± 8.6%, which did not significantly change after training.

Conclusions: Aerobic exercise training improved cardio-pulmonary fitness in patients with ToF but not in patients with Fontan circulation. Exercise training did not change daily physical activity.

INTRODUCTION

Current public health guidelines suggest at least 60 minutes of moderate-to-vigorous physical activity daily for children and adults[1]. Increasing physical activity can improve cardio-pulmonary fitness and a better cardio-pulmonary fitness may promote more physical activity[2]. Among other factors such as diagnosis, NYHA class, age at surgery and peak heart rate, poor cardio-pulmonary fitness, is a risk factor for hospitalization and death in patients with congenital heart disease (ConHD)[3]. Patients with corrected tetralogy of Fallot (ToF-patients) or Fontan circulation (Fontan-patients) are amongst those with the highest risk for late deterioration of cardiac function[4]. These patients are advised to engage in physical activities in concordance with the current public health guidelines[5].

Several studies have examined the effect of physical exercise training programs in patients with ConHD. Training programs that successfully improved cardio-pulmonary fitness had an average duration of 12 weeks, an aerobic intensity level and a minimal training frequency of twice a week for 1 hour[6]. Peak oxygen uptake (peakVO_2) was the most frequently used outcome parameter to assess improvement in physical exercise capacity. These studies, often with small sample sizes and including different ConHD diagnoses as well as ages from 4 up to 40 years, reported a mean increase in peakVO_2 of 2.6 ml/kg/min[6]. However, a randomized controlled trial design was seldom used[6].

Previous studies that measured activity levels objectively demonstrated that only a minority of children with ConHD were moderately-to-vigorously physically active for at least 60 minutes per day[7, 8]. Only two studies included accelerometry assessments to evaluate changes in daily physical activity after an exercise training program. These studies suggested a positive effect of exercise training on daily physical activity in a heterogeneous group of ConHD patients[9, 10]. This contributes to the suggestion that an interaction between daily physical activity and cardio-pulmonary fitness exists[2].

We aimed to assess the effects of a standardized 12 week exercise training program on cardio-pulmonary fitness and daily physical activity in children and young adults with corrected tetralogy of Fallot or Fontan circulation. Both groups were selected in order to create a homogenous study population, all at risk for late deterioration of cardiac function[4]. The duration of the exercise training program was based on the results of previous studies[6]. We hypothesized that exercise training would increase cardio-pulmonary fitness, measured as peakVO_2 and daily physical activity level, measured in metabolic equivalent (MET).

METHODS

Trial design

A multi-center prospective randomized controlled trial was designed according to Consolidated Standards of Reporting Trials (CONSORT) guidelines[11]. Five university hospital congenital cardiology centers in the Netherlands participated (Amsterdam, Leiden, Rotterdam, Nijmegen and Utrecht).

Participants

Patients were identified through local databases of participating hospitals. ToF or Fontan-patients between 10 and 25 years were eligible. Correction of tetralogy of Fallot, using the transatrial-transpulmonary approach, had to be performed before the age of 3.5 years. The Fontan circulation had to be completed before the age of 6 years. All participants had to be able, both mentally as well as physically, to adhere to a training program. Patients with a ventricular outflow obstruction >60 mmHg were excluded, as were patients with general contra-indications for cardiac MRI.

The study complied with the Declaration of Helsinki. Local Ethics Committees approved of the research protocol. All participants, and/or their parents if required, signed a written informed consent. The trial was registered at www.trialregister.nl, identification number NTR2731.

Randomization, allocation and blinding

Participants were randomized in a 2:1 ratio to the exercise-group or control-group. Randomization was performed by an independent blinded researcher. Stratification was based on gender, ConHD and age group (10 - 12, 12 - 15, 15 - 18 and 18 - 25 years). The protocol included cardiac magnetic resonance imaging, (MRI) at rest and with dobutamine stress. Not all patients consented in dobutamine stress MRI. Randomization took place irrespective of the consent whether or not to participate in stress MRI. Only if the entire imaging procedure could be finished within the allocated scan time of 90 minutes did we perform dobutamine stress MRI. Logistics of MRI and stress tests was managed by personnel unaware of the randomization.

Intervention

Based on previous studies, a 12 week standardized aerobic exercise-training program was used[6]. The training program consisted of three one-hour exercise sessions per week which were added to normal daily life activity. The exercise sessions consisted of 40 minutes aerobic dynamic cardiovascular training, ten minutes warming up and ten minutes cooling down. Participants were given a heart rate monitor (SR400, Polar Electro the Netherlands BV, Almere) to help them train within the predetermined submaximal heart

rate range, which was set at the resting heart rate plus 60 - 70% of the heart rate reserve, determined at the baseline cardiopulmonary exercise test. The training program was executed and supervised by a local physiotherapist. An attendance list was kept to monitor adherence to the training sessions. A single researcher visited the participating physiotherapists prior to the program to ensure uniform use for all participants.

The control group was instructed to continue their normal daily life.

Outcome assessments

The outcome assessments took place at the university hospital that followed the patient. The following assessments were made in a time period of two weeks before and two weeks after the exercise training.

Cardio-pulmonary fitness

Cardio-pulmonary fitness was assessed by cardiopulmonary exercise testing. The same locally available ergometer and gas-analyzers were used per patient. The protocol started with 1 minute of unloaded cycling with a cadence of 65 - 75 repetitions per minute. Thereafter load increased by 10, 15 or 20 Watt per minute, depending on height (<150; >150 - 180; >180 cm). All participants were encouraged to continue cycling until exhaustion, defined as the inability to maintain the pre-set repetition rate. The test was marked as maximal effort if the respiratory exchange ratio (RER) during the test phase was higher than 1.0, according to widely accepted guidelines[12]. The following parameters were determined: peakVO_2 (ml/kg/min), averaged over the final 30 seconds of exercise; peak workload (Watt), averaged over the final 60 seconds of exercise; peak minute ventilation (peakVE) (l/min), averaged over the final 30 seconds of exercise; peak heart rate (peakHR) (bpm), highest HR measured during exercise; peak oxygen pulse (peakO_2Pulse) (ml/beat), peakVO_2 divided by peakHR; peak-RER, highest measured RER during exercise; ventilatory anaerobic threshold VO_2 ($VATVO_2$) (ml/kg/min), VO_2 at VAT; minute ventilation to carbon dioxide production slope (VE/VCO_2-slope) (measured from the start of exercise up till the respiratory compensation point) and oxygen uptake efficiency slope (OUES)[13-15].

Stroke volume

Each participant underwent cardiac MR) before and after the intervention period on the locally available whole body MRI. A multi-phase, multi-slice volumetric data set was acquired with either breath-holds (ToF-patients) or averaging 3 heart beats to eliminate the effect of respiration (Fontan-patients)[16]. Low-dose dobutamine stress images were only acquired when logistically possible and if the patient consented[16]. Analysis was performed with software package QMass (Medis Medical Imaging Systems BV, Leiden, the Netherlands). Stroke volume (SV) was indexed for body surface area (BSA). If a

second ventricle existed in Fontan-patients, its SV was added to that of the systemic. Experienced observers analyzed the data according to previously described methods[17].

Daily physical activity

Daily physical activity was measured with an Actigraph GT3X triaxial accelerometer, which has been validated[18]. The subjects wore the accelerometer on their waist for 5 consecutive days, including weekend-days. The tool was removed only for swimming, showering and sleeping. Accelerometer data were only included in analysis in case of a minimum of wear time of 3 days and per day of 8 hours. Data was analyzed with ActiLife 6 software. Counts per minute were converted to MET using age specific formula's by Freedson et al.[19]. MET-values of 3, 6 and 9 were used as lower limits for moderate, vigorous and very vigorous activity, respectively[19]. The subjects' level of physical activity was interpreted as the amount of time spent at each activity level, expressed as percentage of the total measured time, and as the average metabolic equivalent.

Statistical analysis

Sample size calculation was based on the primary endpoint of change in peakVO_2. We calculated that 90 patients were required to obtain 88% power to detect a difference of 20% of peakVO_2 (from 37 ± 10 to 44 ± 10 ml/kg/min) between the intervention and control group, considering a randomization ratio of 2:1 and a two-sided α of 0.05.

Data was tested for normality with Kolmogorov-Smirnov test. Normally distributed data is expressed as mean (± standard deviation (SD)), nonparametric data as median (interquartile range (IQR)). Between subjects comparisons were analyzed by two-way ANOVA, within subjects comparisons were analyzed by paired Student's t-test or Wilcoxon signed rank test if appropriate. Correlation was analyzed using linear regression. Analysis was performed using SPSS statistical software package version 21.

RESULTS

Patients Characteristics

Three hundred and sixty-two patients were contacted to participate in this study (flow chart, figure 1). The time-consuming nature of the study was the main reason for patients not to participate. Age at the time of the study and age at operation did not significantly differ between the participants and non-participants. A total of 93 patients participated in the study. Three patients (3.2%), randomized to the exercise-group, dropped-out. The baseline characteristics did not significantly differ between the exercise-group and the control-group (table 1). In accordance with the inclusion criteria all patients had a ventricular outflow gradient less than 60 mmHg. The maximal outflow gradient measured

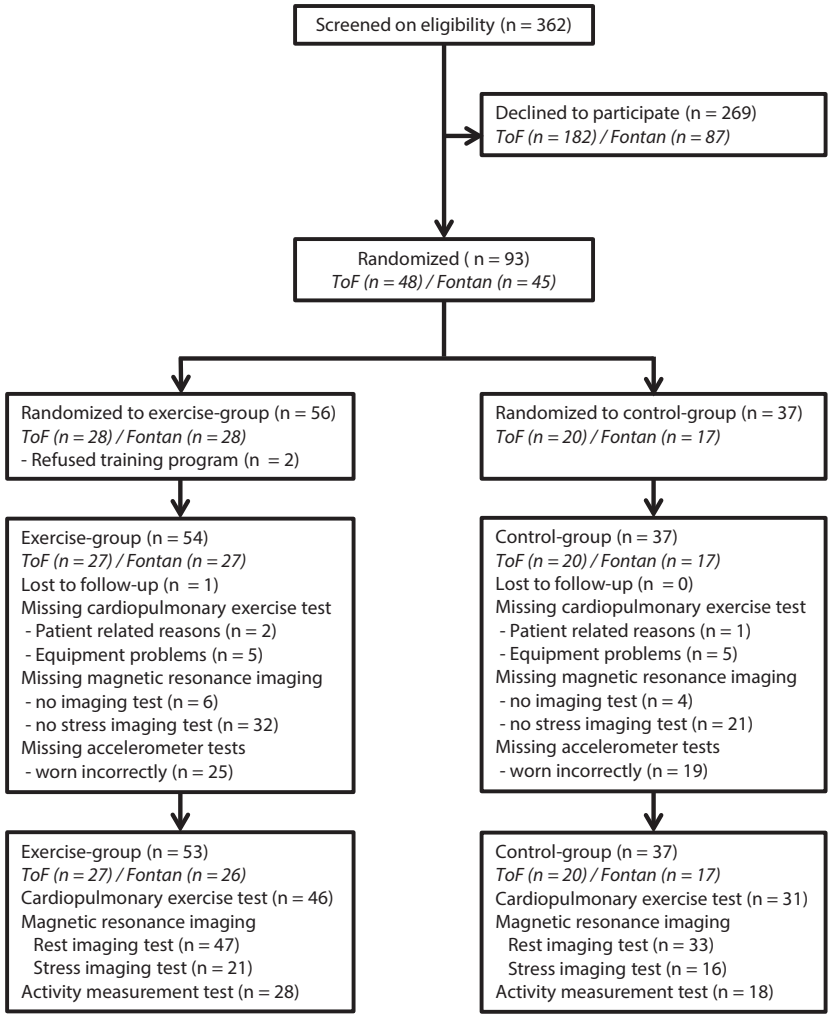


Figure 1: Enrollment

in the participating patients was 37 mmHg. A gradient greater than 30 was measured in 3 patients, 2 in the training group and 1 in the control group.

Training adherence

Fifty-three participants in the exercise-group completed the study protocol. On average 4 training sessions in 12 weeks were missed. Adherence to the training session in the program was 89% (median, IQR 79-100%). To assess adherence to the training intensity level a random sample of recorded heart rate during exercise training was reviewed (n = 11). In all these patients HR was within the set limits.

Table 1: Patient characteristics

	All	Randomization	
	(n = 90)	Exercise-group (n = 53)	Control-group (n = 37)
Male (n)	66 (73%)	40 (76%)	26 (70%)
Age start study (yrs)	15 ± 3	15 ± 3	16 ± 3
Length (cm)	164 ± 13	163 ± 14	166 ± 12
Weight (kg)	55 ± 15	54 ± 15	55 ± 14
O_2-saturation at follow-up (%)	97 (95 - 100)	97 (95 - 99)	98 (95 - 100)
History of arrhythmia (n)	7 (8%)	4 (8%)	3 (8%)
Medication (n)*	6 (7%)	4 (8%)	2 (5%)
NYHA class II †	22 (24%)	12 (23%)	10 (27%)
ToF (n)	47 (52%)	27 (57%)	20 (43%)
Age at ToF correction (months)		6 (4-13)	7.5 (5 - 10)
Follow-up since ToF correction (yrs)		15 ± 2	16 ± 3
Intervention prior ToF correction (n)		8 (30%)	4 (20%)
Intervention post ToF correction (n)		8 (30%)	7 (35%)
Pulmonary regurgitation present (n)		27 (100%)	20 (100%)
Fontan (n)	43 (48%)	26 (60%)	17 (40%)
Dominant ventricle left/right (n)		18 / 8 (69 / 31%)	12 / 5 (71 / 29%)
Fontan type ILT/ECC/other (n)		14 / 11 / 1 (54 / 42 / 4%)	7 / 9 / 1 (41 / 53 / 6%)
Age at Fontan completion (yrs)		3 (2.5 - 4)	3 (2 - 5)
Follow-up since Fontan completion (yrs)		11 ± 4	11 ± 4
Intervention post Fontan completion (n)		5 (19%)	5 (29%)

Yrs years; cm centimeter; kg kilogram O_2 oxygen. *all Fontan-patients used antithrombotic drugs, not shown in table; †all patients are NYHA class I unless shown in table as NYHA class II.

Cardio-pulmonary fitness

All but 3 participants underwent cardiopulmonary exercise testing twice (table 2). Peak values are only presented for patients who successfully completed the test twice with a RER >1.0. Submaximal values are presented for all patients.

All participants, a comparison of the exercise and control groups

In the exercise-group peakVO_2 increased with 5.0% after the exercise training program ($p = 0.011$) whereas the control-group did not show an increase in peakVO_2. The increase of PeakVO_2 was not significantly different between groups. Workload and ventilation (peakVE) significantly increased in the exercise-group compared to the control-group. PeakO_2pulse in the exercise-group increased ($p = 0.001$), whereas the control-group showed no increase. The increase of peakO_2pulse was not significantly different between groups (table 2). The changes in submaximal parameters, VO_2 at VAT, VE/VCO_2-slope and OUES, did not significantly differ between the exercise-group and the control-group (table 2).

Table 2: Results: cardiopulmonary exercise tests

Maximal Tests	All patients					ToF					Fontan				
	Exercise-group (n = 43)		Control-group (n = 30)		Sig.	Exercise-group (n = 24)		Control-group (n = 19)		Sig.	Exercise-group (n = 19)		Control-group (n = 11)		Sig.
	Before	After	Before	After		Before	After	Before	After		Before	After	Before	After	
PeakVO_2(ml/kg/min)	34.2 ± 6.4	35.9 ± 7.4*	33.3 ± 7.8	34.2 ± 8.6	n.s.	35.1 ± 6.7	38.0 ± 7.6*	34.5 ± 8.3	35.2 ± 8.0	n.s.	32.9 ± 5.9	33.2 ± 6.5	31.3 ± 6.8	32.5 ± 9.6	n.s.
Peak workload(watt)	151 ± 54	157 ± 51	148 ± 48	149 ± 47	0.047	170 ± 53	179 ± 50	170 ± 38	170 ± 39	0.048	126 ± 44	131 ± 40	110 ± 39	113 ± 36	n.s.
PeakVE(l/min)	70.6 ± 22.6	78.3 ± 28.9	71.2 ± 21.2	70.7 ± 23.3	0.014	76.2 ± 19.9	86.3 ± 29.1	76.7 ± 22.7	74.8 ± 25.3	0.008	64.2 ± 24.4	68.9 ± 26.5	61.6 ± 14.5	63.6 ± 18.3	n.s.
PeakO_2Pulse(ml/beat)	10.9 ± 2.9	11.9 ± 3.6*	10.4 ± 3.3	11.0 ± 3.3	n.s.	12.1 ± 2.8	13.4 ± 3.4*	11.5 ± 3.4	12.0 ± 3.3	n.s.	9.5 ± 2.5	9.7 ± 2.6	8.6 ± 2.1	9.3 ± 2.8	n.s.
PeakHR(beats/min)	175 ± 16	175 ± 15	178 ± 19	176 ± 18	n.s.	180 ± 13	178 ± 16	181 ± 17	180 ± 13	n.s.	169 ± 17	172 ± 13	172 ± 23	168 ± 23	n.s.
Peak-RER	1.12 ± 0.06	1.14 ± 0.08	1.14 ± 0.08	1.13 ± 0.07	n.s.	1.13 ± 0.07	1.13 ± 0.08	1.16 ± 0.08	1.15 ± 0.07	n.s.	1.10 ± 0.05	1.14 ± 0.08	1.12 ± 0.07	1.11 ± 0.07	n.s.
Submaximal Tests															
	Exercise-group (n = 46)		Control-group (n = 31)			Exercise-group (n = 24)		Control-group (n = 19)			Exercise-group (n = 22)		Control-group (n = 12)		
VAT VO_2(ml/kg/min)	22.2 ± 7.9	20.9 ± 5.9	20.6 ± 6.0	20.6 ± 6.2	n.s.	20.8 ± 7.2	22.4 ± 6.5	20.2 ± 6.3	19.8 ± 6.2	n.s.	23.8 ± 8.5	19.3 ± 4.7	21.2 ± 5.7	21.9 ± 6.3	0.038
VE/VCO_2-slope	28.8 ± 5.1	29.5 ± 6.4	29.6 ± 6.6	29.3 ± 6.5	n.s.	26.5 ± 4.0	27.7 ± 5.0	26.2 ± 3.7	26.3 ± 4.5	n.s.	31.3 ± 5.2	31.4 ± 7.4	35.1 ± 6.5	34.3 ± 6.2	n.s.
OUES	2196 ± 616	2180 ± 615	2049 ± 603	2175 ± 676	n.s.	2431 ± 656	2513 ± 599	2289 ± 567	2397 ± 639	n.s.	1937 ± 455	1814 ± 388	1670 ± 459	1823 ± 597	0.009

VO_2 oxygen uptake; VE minute ventilation; O2Pulse oxygen pulse; HR heart rate; RER respiratory exchange ratio; VAT ventilatory anaerobic threshold; VE/VCO_2 minute ventilation in relation to carbon dioxide production; OUES oxygen uptake efficiency slope. Within group analysis with paired t-tests,* $p < 0.05$; between group analysis with 2-way ANOVA; n.s. not significant.

The changes in blood pressures from the baseline measurements to the post intervention measurements from rest (113 ± 13 / 73 ± 11 mmHg) to peak exercise (165 ± 31 / 71 ± 14 mmHg) and from peak exercise to recovery (135 ± 22 / 68 ± 14 mmHg) did not significantly change, nor differ between the exercise-group and the control-group.

ToF-patients

PeakVO_2 in the ToF-patients allocated to the exercise-group increased with 8.3% after the exercise training program ($p = 0.002$) whereas peakVO_2 in the control-group did not increase. The increase in PeakVO_2 was not significantly different between groups. Workload and ventilation (peakVE) significantly increased in the exercise-group compared to the control-group. PeakO_2pulse in the exercise-group increased ($p < 0.001$), whereas peakO_2pulse in the control-group did not increase. The increase in peakO_2pulse was not significantly different between groups. The changes in submaximal parameters, VAT VO_2, VE/VCO_2-slope and OUES did not significantly differ between the exercise-group and the control-group.

Fontan-patients

PeakVO_2 did not significantly increase after the exercise training program in the Fontan-patients in the exercise-group as well as the control-group. The change in peakVO_2, peakload, peakVE and peakO_2pulse after the exercise training program did not significantly differ between the exercise-group and the control-group (Table 2). Within the submaximal parameters, VO_2 at VAT and OUES significantly changed between the exercise-group and the control-group, whereas VE/VCO_2-slope did not significantly change between the groups.

Stroke volume

Indexed stroke volumes (SV_i), as assessed with MRI, are shown before and after the exercise training program in figure 2.

ToF-patients (regardless of randomization) had a SV_i before the exercise training program at rest of 50.2 ± 6.5 ml/m^2, which significantly increased with dobutamine stress to 61.0 ± 9.0 ml/m^2. After the exercise training program SV_i at rest was 48.0 ± 7.8 ml/m^2, which significantly increased at dobutamine stress to 59.9 ± 11.4 ml/m^2. The exercise training program did not affect the SV_i or SV_i increase from rest to dobutamine stress.

Fontan-patients (regardless of randomization) had a SV_i before the exercise training program at rest of 51.1 ± 8.8 ml/m^2 and at dobutamine stress of 53.3 ± 13.0 ml/m^2. After the exercise training program the SV_i at rest was 50.0 ± 9.2 ml/m^2 and at dobutamine stress 51.4 ± 12.4 ml/m^2. SV_i did not significantly increase in the exercise-group or control-group in Fontan-patients, either from rest to dobutamine stress or from pre-to-post exercise training program.

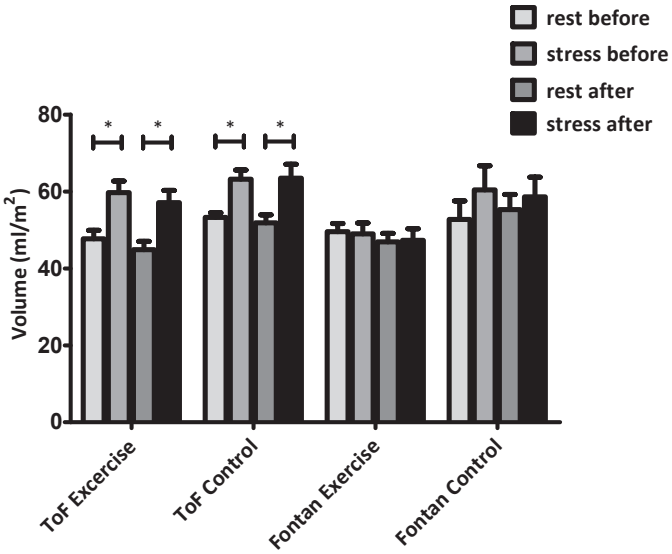


Figure 2: Stroke volume
Bar represents stroke volume indexed by BSA (ToF-patients: left ventricle) *: $p < 0.05$.

Daily physical activity

Twenty-eight patients in the exercise group and 18 patients in the control group were included in daily physical activity analyses (table 3). Time spent sedentary or in moderate-to-very-vigorous activity measured at baseline did not significantly differ between the exercise group and control group nor did it change after the intervention period. Time spent in moderate-to-very-vigorous activity at baseline, regardless of randomization was 13.6 ± 8.6% of the registered time, which was 104 ± 65 minutes per day. At baseline 30% of all patients did not meet the guidelines of 60 minutes of moderate-to-vigorous activity, which did not change significantly after the training program.

Table 3: Activity measurements

	Exercise-group (n = 28)		Control-group (n = 18)		Sig.
Parameters	Before	After	Before	After	
MET's	1.7 ± 0.4	1.7 ± 0.4	1.6 ± 0.3	1.6 ± 0.3	n.s.
Time spent sedentary(%)	67.6 ± 13.0	69.6 ± 11.7	69.4 ± 10.4	69.4 ± 10.8	n.s.
Time spent in moderate-to-very-vigorous activity(%)	14.8 ± 9.5	12.7 ± 8.1	11.8 ± 6.8	11.8 ± 6.2	n.s.

MET metabolic equivalent; n.s. not significant. The amount of time spent is expressed as percentage of the total measured time. Within group analysis with paired t-tests,*$p < 0.05$; between group analysis with 2-way ANOVA.

DISCUSSION

This randomized controlled trial demonstrated that 12 weeks of exercise training significantly increased peak VO_2 in ToF-patients, although this did not significantly differ from the control group. However, the significant increase in workload and ventilation in the ToF exercise-group in comparison to the control-group point in the direction of improved cardio-pulmonary fitness. In contrast the Fontan-patients did not increase their cardiopulmonary fitness after training. In addition, we demonstrated that exercise training did not alter daily physical activity in any of the groups.

Cardio-pulmonary fitness

Strict supervision and monitoring of the training sessions and of training intensity level assured that the required training effort was delivered. This is reflected in our below average drop out percentage (3%) in comparison to a mean of 16% in previous exercise studies in ConHD[6]. Compared to previous studies, training adherence in our participants (89%) was above the reported average of 80%[6].

The significant increase in peakVO_2 of 3 ml/kg/min (5%) in our ToF-patients is in the same range as reported in a pilot study with adult ToF-patients as well as in other exercise studies among heterogeneous groups of ConHD patients and exercise studies in healthy adolescents (5 - 6%)[6, 20, 21]. In contrast, 2 previous exercise studies involving children with ToF were unable to demonstrate a significant increase in peakVO_2. This may have been related to the small number of participants (<12) included in those studies as well as a less vigorous training program[22, 23].

Our data on the changes in stroke volume with dobutamine stress and on peakO_2Pulse indicate that ToF-patients can increase heart rate as well as stroke volume when exercise demands an increased cardiac output. This may have contributed to the increased cardio-pulmonary fitness in response to aerobic exercise training[24].

In contrast to the ToF-patients, Fontan-patients did not increase their peakVO_2 after exercise training. This observation is in contrast with most previous exercise studies in adult Fontan-patients as well as in 3 out of 4 exercise studies in younger Fontan-patients[25-29]. The most likely explanation for these contrasting findings may be related to the low baseline peakVO_2 of 25 - 28 ml/kg/min in previous studies compared to a baseline peakVO_2 of 33 ml/kg/min in our study. A relatively high baseline of physical exercise capacity may hamper an increase in cardio-pulmonary fitness by training. In a cross sectional study in our institutions a similar peakVO_2 of 33 ± 8 ml/kg/min was observed in Fontan-patients[30]. We, therefore, think inclusion bias for our exercise study towards the fitter patients is unlikely.

The data on the changes in stroke volume with dobutamine stress indicate that Fontan patients were not able to increase stroke volume, which was not altered by the exercise

training intervention. The lack of increase in stroke volume most likely relates to preload impairment in the Fontan circulation[16]. This suggests that when exercise demands an increased cardiac output, this will result in a limited increase in stroke volume, and therefore limitation of exercise capacity in Fontan patients. We, therefore, speculate that Fontan-patients may reach a plateau in their capability to enhance stroke volume and thus cardiac output, which may reduce the potential increase in peakVO_2 with aerobic exercise training.

Daily physical activity

Seventy percent of our patients were moderately to vigorously active for more than 60 minutes per day at baseline, which is in concordance with the reported 76% of moderately to vigorously active ConHD patients by Muller et al[31]. Other studies have reported much lower percentages[7, 8]. This observation may in part explain the difference in baseline physical fitness between our study and previous studies. Physical activity may be related to geographic location and associated cultural differences; for instance, in the Netherlands many, if not all, adolescents ride a bicycle as means of transport to and from school.

Morrison et al. noted an increase in activity levels after exercise intervention, which was accompanied by psychological motivational techniques[10]. Since it is well-known that changing lifestyle is difficult, a multidisciplinary approach may be required to successfully change daily physical activity levels[32]. Based on the results of our study, with already 70% of patients adhering to at least 60 minutes of daily activity, a change in activity level cannot be achieved by an exercise training program alone in children and young adults ToF or Fontan-patients. An increase in cardio respiratory fitness, like in the ToF exercise group, does not directly result in an increase in daily physical activity.

Limitations

Since this was a multi-center trial we had to use different set-ups for exercise testing in our study. However, we do not think that this has affected our main outcome measures, since all centers used the same protocol, had state of the art equipment and, moreover, patients served as their own controls. In the present study we focused on aerobic exercise training. Considering our results, aerobic exercise is adequate to improve physical fitness in ToF patients. In Fontan patients, other types of exercise may require further study. The geographic location of the study may have influenced the activity level results as Dutch children commonly commute by bicycle which is not custom in most other countries. Although we did not find major differences between participants and non-participants in the study, we cannot rule out inclusion bias towards more fit patients. Patients with irregular heart rhythm were excluded from MRI, since this is a general contra-indication for cardiac MRI. However, the presence of arrhythmias may have limited inclusion of

subjects into the study in general. Age may be a factor in the effects of exercise training. Our study lacks statistical power to demonstrate an age effect.

Contrary to the situation in adults with congenital heart disease there is no consensus on the optimal RER value to determine maximal exercise in exercise testing[33]. Different cut-off values of the RER have been used in various studies that have focused on the change of peakVO_2 due to an exercise training program in children. In these studies RER cut-off values have varied from 1.1[34-37]. The results of our study did not change if we used a RER of 1.05 or 1.1.

Conclusion

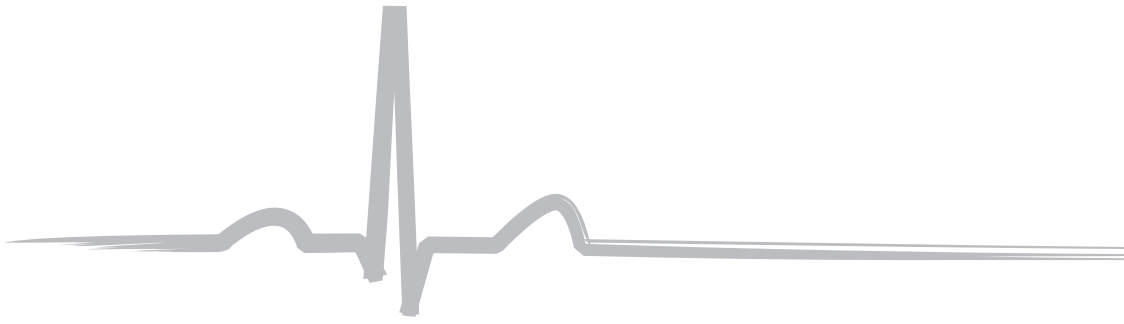
Twelve weeks of aerobic exercise training improved physical performance in ToF-patients but not in Fontan-patients, while it did not alter daily physical activity in both groups.

REFERENCES

1. Strong WB, Malina RM, Blimkie CJ, Daniels SR, Dishman RK, Gutin B, Hergenroeder AC, Must A, Nixon PA, Pivarnik JM, Rowland T, Trost S, Trudeau F. Evidence based physical activity for school-age youth. *J Pediatr*. 2005;146:732-737
2. Ortega FB, Ruiz JR, Castillo MJ, Sjostrom M. Physical fitness in childhood and adolescence: A powerful marker of health. *Int J Obes (Lond)*. 2008;32:1-11
3. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: Comparative severity, correlates, and prognostic implication. *Circulation*. 2005;112: 828-835
4. Norozi K, Wessel A, Alpers V, Arnhold JO, Geyer S, Zoege M, Buchhorn R. Incidence and risk distribution of heart failure in adolescents and adults with congenital heart disease after cardiac surgery. *Am J Cardiol*. 2006;97:1238-1243
5. Takken T, Giardini A, Reybrouck T, Gewillig M, Hovels-Gurich HH, Longmuir PE, McCrindle BW, Paridon SM, Hager A. Recommendations for physical activity, recreation sport, and exercise training in paediatric patients with congenital heart disease: A report from the exercise, basic & translational research section of the european association of cardiovascular prevention and rehabilitation, the european congenital heart and lung exercise group, and the association for european paediatric cardiology. *Eur J Prev Cardiol*. 2012;19:1034-1065
6. Duppen N, Takken T, Hopman MT, ten Harkel AD, Dulfer K, Utens EM, Helbing WA. Systematic review of the effects of physical exercise training programmes in children and young adults with congenital heart disease. *Int J Cardiol*. 2013;168:1779-1787
7. Arvidsson D, Slinde F, Hulthen L, Sunnegardh J. Physical activity, sports participation and aerobic fitness in children who have undergone surgery for congenital heart defects. *Acta Paediatr*. 2009; 98:1475-1482
8. Massin MM, Hovels-Gurich HH, Gerard P, Seghaye MC. Physical activity patterns of children after neonatal arterial switch operation. *Ann Thorac Surg*. 2006;81:665-670
9. Fredriksen PM, Kahrs N, Blaasvaer S, Sigurdsen E, Gundersen O, Roeksund O, Norgaand G, Vik JT, Soerbye O, Ingjer E, Thaulow E. Effect of physical training in children and adolescents with congenital heart disease. *Cardiol Young*. 2000;10:107-114
10. Morrison ML, Sands AJ, McCusker CG, McKeown PP, McMahon M, Gordon J, Grant B, Craig BG, Casey FA. Exercise training improves activity in adolescents afflicted with congenital heart disease. *Heart*. 2013;99(15):1122-1128
11. Schulz KF, Altman DG, Moher D, Group C. Consort 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332
12. Armstrong N, van Mechelen W. Aerobic fitness. *Paediatric exercise science and medicine*. Oxford: Oxford University Press; 2008:97-108.
13. Bongers B, Hulzebos H, Blank A, van Brussel M, Takken T. The oxygen uptake efficiency slope in children with congenital heart disease: Construct and group validity. *Eur J Cardiovasc Prev Rehabil*. 2011;18 (3):384-392
14. Ohuchi H, Nakajima T, Kawade M, Matsuda M, Kamiya T. Measurement and validity of the ventilatory threshold in patients with congenital heart disease. *Pediatr Cardiol*. 1996;17:7-14
15. Giardini A, Odendaal D, Khambadkone S, Derrick G. Physiologic decrease of ventilatory response to exercise in the second decade of life in healthy children. *Am Heart J*. 2011;161:1214-1219

16. Robbers-Visser D, Jan Ten Harkel D, Kapusta L, Strengers JL, Dalinghaus M, Meijboom FJ, Pattynama PM, Bogers AJ, Helbing WA. Usefulness of cardiac magnetic resonance imaging combined with low-dose dobutamine stress to detect an abnormal ventricular stress response in children and young adults after fontan operation at young age. *Am J Cardiol*. 2008;101:1657-1662
17. Robbers-Visser D, Boersma E, Helbing WA. Normal biventricular function, volumes, and mass in children aged 8 to 17 years. *J Magn Reson Imaging*. 2009;29:552-559
18. de Vries SI, Bakker I, Hopman-Rock M, Hirasing RA, van Mechelen W. Clinimetric review of motion sensors in children and adolescents. *J Clin Epidemiol*. 2006;59:670-680
19. Freedson P, Pober D, Janz KF. Calibration of accelerometer output for children. *Med Sci Sports Exerc*. 2005;37:S523-530
20. Therrien J, Fredriksen P, Walker M, Granton J, Reid GJ, Webb G. A pilot study of exercise training in adult patients with repaired tetralogy of fallot. *Can J Cardiol*. 2003;19:685-689
21. Baquet G, van Praagh E, Berthoin S. Endurance training and aerobic fitness in young people. *Sports Med*. 2003;33:1127-1143
22. Calzolari A, Turchetta A, Biondi G, Drago F, De Ranieri C, Gagliardi G, Giambini I, Giannico S, Kofler AM, Perrotta F, et al. Rehabilitation of children after total correction of tetralogy of fallot. *Int J Cardiol*. 1990;28:151-158
23. Sklansky MS, Pivarnik JM, O'Brian Smith E, Morris J, Bricker JT. Exercise training hemodynamics and the prevalence of arrhythmia's in children following tetralogy of fallot repair. *Pediatric Exercise Science*. 1994;6:188-200
24. van den Berg J, Wielopolski PA, Meijboom FJ, Witsenburg M, Bogers AJ, Pattynama PM, Helbing WA. Diastolic function in repaired tetralogy of fallot at rest and during stress: Assessment with mr imaging. *Radiology*. 2007;243:212-219
25. Cordina RL, O'Meagher S, Karmali A, Rae CL, Liess C, Kemp GJ, Puranik R, Singh N, Celermajer DS. Resistance training improves cardiac output, exercise capacity and tolerance to positive airway pressure in fontan physiology. *Int J Cardiol*. 2013;168:780-788
26. Winter MM, van der Bom T, de Vries LC, Balducci A, Bouma BJ, Pieper PG, van Dijk AP, van der Plas MN, Picchio FM, Mulder BJ. Exercise training improves exercise capacity in adult patients with a systemic right ventricle: A randomized clinical trial. *Eur Heart J*. 2012;33:1378-1385
27. Minamisawa S, Nakazawa M, Momma K, Imai Y, Satomi G. Effect of aerobic training on exercise performance in patients after the fontan operation. *Am J Cardiol*. 2001;88:695-698
28. Opocher F, Varnier M, Sanders SP, Tosoni A, Zaccaria M, Stellin G, Milanesi O. Effects of aerobic exercise training in children after the fontan operation. *Am J Cardiol*. 2005;95:150-152
29. Singh TP, Curran TJ, Rhodes J. Cardiac rehabilitation improves heart rate recovery following peak exercise in children with repaired congenital heart disease. *Pediatr Cardiol*. 2007;28:276-279
30. Robbers-Visser D, Kapusta L, van Osch-Gevers L, Strengers JL, Boersma E, de Rijke YB, Boomsma F, Bogers AJ, Helbing WA. Clinical outcome 5 to 18 years after the fontan operation performed on children younger than 5 years. *J Thorac Cardiovasc Surg*. 2009;138:89-95
31. Muller J, Hess J, Hager A. Daily physical activity in adults with congenital heart disease is positively correlated with exercise capacity but not with quality of life. *Clin Res Cardiol*. 2012;101:55-61
32. Giannakoulas G, Dimopoulos K. Exercise training in congenital heart disease: Should we follow the heart failure paradigm? *Int J Cardiol*. 2010;138:109-111
33. Rhodes J, Ubeda Tikkanen A, Jenkins KJ. Exercise testing and training in children with congenital heart disease. *Circulation*. 2010;122:1957-1967

34. Amiard V, Jullien H, Nassif D, Bach V, Maingourd Y, Ahmaidi S. Effects of home-based training at dyspnea threshold in children surgically repaired for congenital heart disease. *Congenit Heart Dis*. 2008;3:191-199
35. Brassard P, Poirier P, Martin J, Noel M, Nadreau E, Houde C, Cloutier A, Perron J, Jobin J. Impact of exercise training on muscle function and ergoreflex in fontan patients: A pilot study. *Int J Cardiol*. 2006;107:85-94
36. Balfour IC, Drimmer AM, Nouri S, Pennington DG, Hemkens CL, Harvey LL. Pediatric cardiac rehabilitation. *Am J Dis Child*. 1991;145:627-630
37. Moalla W, Elloumi M, Chamari K, Dupont G, Maingourd Y, Tabka Z, Ahmaidi S. Training effects on peripheral muscle oxygenation and performance in children with congenital heart diseases. *Appl Physiol Nutr Metab*. 2012;37:621-630



Chapter 5

The effect of exercise training on cardiac remodeling in children and young adults with corrected tetralogy of Fallot or Fontan circulation: a randomized controlled trial.

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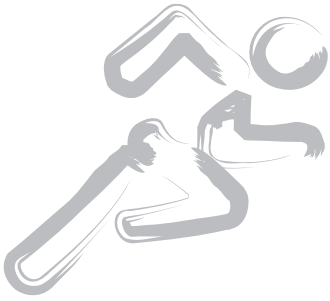

ABSTRACT

Background: Exercise can improve physical fitness in children and adults with congenital heart disease. We hypothesized that exercise training would not lead to adverse cardiac remodeling in this population.

Methods and results: This multi-center randomized controlled trial included children and young adults (10 to 25 years) with either corrected tetralogy of Fallot or Fontan circulation. The exercise-group was enrolled in a 12 week standardized aerobic dynamic exercise training program. The control-group continued their life-style and received care as usual. Both groups underwent cardiopulmonary exercise testing, cardiac magnetic resonance imaging (MRI), echocardiography and neurohormonal assessment, within 2 weeks before and 2 weeks after the intervention period. Fifty-six patients were randomized to the exercise-group, 37 to the control-group. We assessed changes between the pre-and post-intervention period for the exercise group compared to the changes in the control-group. Peak load increased significantly in the exercise-group compared to the control-group (exercise-group 6.9 ± 11.8 Watt; control-group 0.8 ± 13.9 Watt; $p = 0.047$). There were no adverse events linked to the study. Ventricular systolic parameters, cardiac dimensions and neurohormonal markers during follow-up did not change in patients allocated to the exercise-group and control-group. Although there were some isolated minor changes in inflow parameters, there was no consistent pattern of changes, indicating a lack of true change in the diastolic function.

Conclusion: We demonstrated that no clinically relevant adverse cardiac remodeling occurred after 12 weeks exercise training in patients with either corrected tetralogy of Fallot or Fontan circulation.

INTRODUCTION

The long-term prognosis for patients with congenital heart disease (ConHD) has increased considerably in recent years. However, reduced exercise performance and increased risk of cardiovascular diseases are common problems facing this population[1]. Current public-health guidelines state that exercise has to be performed and encouraged even in patients with ConHD[2, 3]. However, many patients with ConHD do not exercise, partly out of fear and from overprotection of peers and parents[4]. In addition, practitioners taking care of these patients may be reluctant to advise physical exercise. Limited knowledge on adverse cardiac events during exercise as well as the effect of exercise on cardiac remodeling in these patients may hamper executing these public-health guidelines[5].

Cardiac size and function may change by exercise. In healthy individuals, including children, exercise results in enhancement of function and adaptive hypertrophy (physiological cardiac remodeling)[6-8]. It is currently unknown if exercise in patients with ConHD will also result in physiological cardiac remodeling or in adverse cardiac remodeling, the latter resulting in an enlarged heart with decreased cardiac function[6, 7].

Various studies have evaluated the effects of exercise training in adolescents and young adults with ConHD. While most of these studies demonstrated that exercise performance can be improved in patients with ConHD, effects on cardiac remodeling have hardly been studied[9].

Patients with tetralogy of Fallot and with a Fontan circulation are amongst those with the highest chance of developing heart failure[1]. Thus these patients may be considered candidates to benefit most from exercise training, but at the same time may be at the highest risk for adverse remodeling in response to exercise training.

Therefore, we aimed to assess the effects of a 12 week standardized aerobic dynamic exercise training program on cardiac remodeling in children and young adults with corrected tetralogy of Fallot (ToF patients) and with Fontan circulation (Fontan patients). We hypothesized that exercise training would not lead to clinically relevant adverse cardiac remodeling.

METHODS

Design

A multi-center prospective, randomized controlled trial was conducted in 5 tertiary referral centers for ConHD in the Netherlands (Academic Medical Centre in Amsterdam, Leiden University Medical Centre in Leiden, Erasmus MC-Sophia in Rotterdam, Radboud University Nijmegen Medical Centre in Nijmegen and University MC Utrecht-Wilhelmina

Children's Hospital in Utrecht). The study was designed according to Consolidated Standards of Reporting Trials (CONSORT) guidelines[10].

Participants

Eligible were adolescents between the age of 10 to 25 years with either corrected tetralogy of Fallot or Fontan circulation. Surgical correction of tetralogy of Fallot had to be performed before the age of 3.5 years through a transatrial-transpulmonary approach. The Fontan circulation had to be completed before the age of 6 years. Patients with ventricular outflow tract obstruction greater than 60 mmHg were excluded, as were all participants who were mentally unable to follow a training program.

Patients were identified through the local databases of the participating hospitals. The study complied with the Declaration of Helsinki. Institutional Ethics Committees of all participating centers approved the research protocol. All participants (and/or their parents if required) signed a written informed consent.

Intervention

Randomization of participants was performed on a 2:1 ratio to either the exercise or control-group by an independent blinded researcher. Stratification was done based on gender, congenital heart defect, and age group (10 - 12 years, 13 - 14 years, 15 - 17 years, and 18 - 25 years). The exercise-group was enrolled in a 12 week standardized aerobic dynamic exercise training program with three 1-hour sessions per week. The training hour was divided in 40 minutes of aerobic dynamic training, and 10 minutes of both warming up and cooling down. The dynamic aerobic exercise training consisted of cardiopulmonary exercises. Participants were given a heart rate monitor (SR400, Polar Electro BV, the Netherlands) to help them perform their exercises within the predetermined submaximal heart rate range. The heart rate monitor would produce an audible signal if the heart rate was outside the set range during training. This range was set at 60 to 70 percent of the heart rate reserve, which was determined by cardiopulmonary exercise test prior to the training program.

The training sessions took place at a local fitness center and were supervised directly by a local physiotherapist. An attendance list was kept and patients were encouraged to participate in all the prescribed sessions. A single researcher visited all the participating physiotherapists prior to the start of the program to ensure that the information and instructions were well understood and standardized implementation of the program occurred. The control-group was instructed to continue their normal daily life.

Cardio-respiratory fitness

Within a range of two weeks before and two weeks after the period of standardized exercise training cardio-respiratory fitness was assessed. Cardiopulmonary exercise tests

were performed to assess peak load and peak oxygen uptake (peakVO_2). Each patient performed the two tests on the same ergometer and gas-analyzers before and after the 12 week period. Locally available ergometers and gas-analyzers were utilized. A modified Bruce exercise protocol was used, with settings adjusted to age, height and gender. All participants were encouraged to continue until exhaustion, defined as inability to maintain 65 rotations per minute. The test was marked as successful if a respiratory exchange ratio (RER) during the maximal test phase of at least 1.0 was attained, according to common guidelines[11].

Adverse events

Adverse events were defined as: death, hospitalization for cardiac reasons and or unplanned doctor visits.

Outcome measurements

Outcome assessments took place at the local center. Within a range of two weeks before and two weeks after the period of standardized exercise training cardiac magnetic resonance imaging, echocardiography and neurohormonal status were measured as described below.

Magnetic resonance imaging

All participants underwent cardiac magnetic resonance imaging (MRI) on the locally available whole body MRI scanners (Philips Panorama UFO 1T, the Netherlands; Siemens Avanto 1.5T, Germany; GE Signa MR/I 1.5T, USA; GE Discovery MR 450, USA; Philips Geva, the Netherlands and Philips Ingenia 4.0, the Netherlands). A multi-phase, multi-slice volumetric data set was acquired using a fast 2D cine scan using steady-state free precession (SSFP). The whole heart from base to apex was covered as described before[12]. All images were acquired with either breath-holds (ToF patients) or over 3 heart beats to eliminate the effect of respiration (Fontan patients). In addition, a standard pulmonary artery localizer scan was obtained. This localizer was used to plan flow measurement perpendicular to main pulmonary artery flow, using phase-contrast velocity-encoding imaging. Analysis was performed with the software packages QMASS and QFLOW (Medis Medical Imaging Systems, the Netherlands). From the short-axis cine-set end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF) and mass were assessed. From the phase-contrast set pulmonary forward flow and regurgitation were assessed. All assessments were executed with manual contour detection. Results are shown by ventricle and are indexed for body surface area (BSA). MRI results of Fontan patients are shown as single ventricle, regardless of their dominant ventricle or a possible second ventricle. If a second ventricle existed, the volume was assessed and added to the systemic ventricle and presented as a single ventricle. All MRI

results were obtained from analysis by experienced observers according to previously described methods[12]. Intra- and interobserver variation for these assessments have been reported[12].

Echocardiography

All participants underwent transthoracic echocardiography, performed by experienced echocardiographic technicians and supervised by a member of the research team. Images were collected with an appropriate transducer, based on age and weight of the participant. Each study was performed at rest on locally available machines (GE Vivid7 Dimension or Vivid E9., USA and Phillips iE33, The Netherlands). Images were recorded and analyzed using offline Xcerlera (Philips, the Netherlands) and EchoPac (GE healthcare, USA). Five consequent heart beats were recorded.

Images were obtained according to a strict protocol according to common guidelines[13]. We measured the following cardiac dimensions in ToF patients: interventricular septum thickness in diastole (IVSd) and systole (IVSs), right ventricle internal diameter in diastole (RVIDd) and systole (RVIDs) and cardiac function, expressed as shortening fraction, all measured according to Lang et al.[14]. Left ventricular wall stress was calculated according to Mizuno et al.[15]. We measured the following cardiac parameters in all patients: maximum velocity in the aorta, pulmonary artery, right upper pulmonary vein (RUPV) and across the mitral and tricuspid valves, as well as deceleration time of peak velocity across the mitral and tricuspid valves, using optimal Doppler settings. M-mode was used to assess maximal mitral and tricuspid annular plane systolic excursions (MAPSE and TAPSE), using common guidelines[13, 14].

In Fontan patients, the velocity in the ascending aorta, RUPV, across the mitral or tricuspid valve, deceleration time of peak velocity across the mitral or tricuspid valve and the annular plane systolic excursion (APSE) were measured for the dominant ventricle.

All parameters were analyzed in 3 cardiac cycles and reported as average over these 3 cycles.

Neurohormonal assessment

Blood samples were collected without the use of a tourniquet from a peripheral vein following 30 minutes of rest after insertion of the cannula. The sample was centrifuged within 30 minutes after collecting and stored at minus 80 degrees. Measurements were performed in one laboratory (Erasmus MC). The following markers were assessed; N-terminal pro-brain natriuretic peptide (NT-proBNP) (Cobas 8000 c702, Roche, the Netherlands), catecholamines (HPLC with fluorometric detection) and plasma aldosterone concentration (radioimmunoassay, Coat-a-Count, Diagnostic Products Corporation, USA), plasma renin (radioimmunoassay (Cisbio Bioassays, France)).

Sample size calculation

Endpoints of our study were: changes (from baseline to 12 weeks follow-up) in 1) left-and right- or single ventricular dimensions, 2) ventricular ejection fraction and 3) NT-proBNP levels. We needed 48 patients in the exercise-group and 24 in the control-group, in order to obtain 90% power ($\beta = 0.10$) to reveal differences of at least ½ standard deviation (SD) in these 3 endpoints between exercise and control-groups (2:1 randomization) ($\alpha = 0.05$, 2-sided test). We took into account a failure-rate of 20% to obtain follow-up measurements. Hence, we decided to enroll 90 patients.

Statistical analysis

Normality of continuous data was evaluated by Kolmogorov-Smirnov tests. The variables NT-proBNP, renine adrenaline, noradrenaline, aldosterone and dopamine were log-transformed in order to obtain a normal distribution. Data with a normal distribution are expressed as mean ± SD, whereas skewed data are presented as median and interquartile range (IQR). Differences in endpoints between exercise and control-groups were analyzed by two-way (repeated measures) analysis of variance (ANOVA), or Wilcoxon-Mann-Whitney tests (using the individual patient's baseline-to-follow-up changes). The differences between the pre and post intervention assessment as well as the difference between the differences of the exercise and control-group are presented as mean and 95% confidence interval (CI). Within subject comparisons were performed by paired Student's t-tests or Wilcoxon signed ranks test, when appropriate. We considered a *p*-value of less than 0.05 (2-sided test) as statistically significant. All statistical analyses were performed using SPSS statistical software package version 21.

RESULTS

Patient characteristics

Three hundred and sixty-two patients were contacted to participate in this study. Age and age at ToF repair or Fontan circulation did not significantly change between participants and those that declined to participate. Ninety-three patients were randomized to either the exercise or the control-group. Three patients in the exercise-group dropped out, due to the demanding study design (Figure 1, flow chart). Patient characteristics of the 90 participants did not differ between the exercise and control-group (Table 1). All patients with a Fontan circulation were on either on oral anticoagulants or platelet inhibitors. In addition 6 Fontan patients (3 in the exercise-group) were on antiarrhythmic drug therapy during the trial period. Medication was unchanged during the study period.

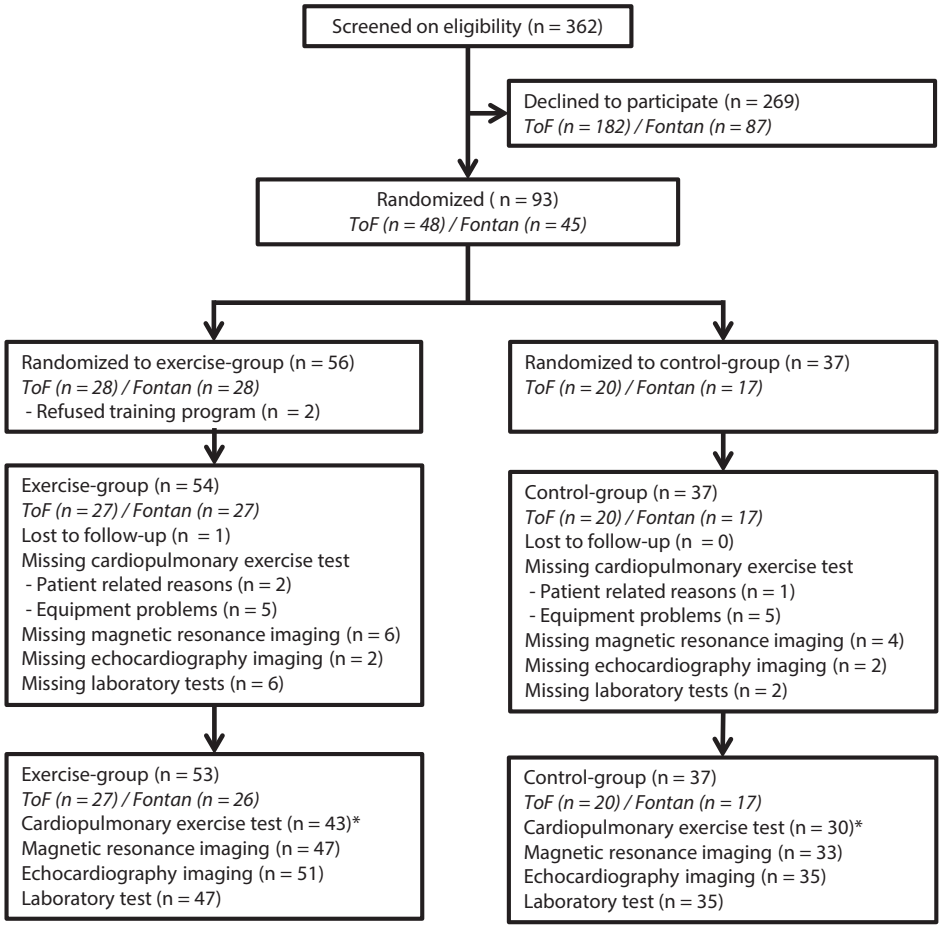

Figure 1: Enrollment
CPET: cardiopulmonary exercise test; * test only included in the analysis if a maximal effort was reached.

Training adherence

Fifty-three patients were randomized to the exercise-group. An attendance rate of 89% (median; IQR 79 - 100%) was achieved by the exercise-group. On average 2.3 training sessions per week were attended. One patient did not attend any of the training program sessions. In a random sample of patients in the exercise-group (n = 11, 21% of all patients randomized to the exercise-group) heart rate data of all recorded training sessions were reviewed. Heart rate during training was within or above the set heart rate range in all reviewed patients.

Table 1: Patient characteristics

Characteristic	ToF (n = 47)	Fontan (n = 43)
Male (n)	35 (74.5%)	31 (72.1%)
Age at start study (years)	16.1 ± 2.6	14.8 ± 3.7
Length (cm)	168 ± 11	160 ± 14
Weight (kg)	58.8 ± 13.2	50.1 ± 14.9
Oxygen saturation at follow-up (%)	100 (98-100)	95 ± 2
NYHA-class I / II	37 / 10 (79% / 21%)	31 / 12 (72% / 28%)
Age at ToF operation (months)	7.5 (4 - 10.5)	
Follow-up time since ToF operation (years)	15.2 ± 2.5	
Pulmonary regurgitation presence (n)	46 (98%)	
Age at Fontan completion (years)		3 (2.5 - 4.4)
Follow-up time since Fontan completion (years)		10.3 (9.0 - 13.0)
Fontan type		
Intra atrial lateral tunnel		21 (48.8%)
Extra cardiac conduit		20 (46.5%)
Other		2 (4.7%)
Dominant ventricle (n)		
Left		30 (69.8%)
Right		13 (30.2%)

ToF: patients with corrected tetralogy of Fallot; Fontan: patients with Fontan circulation. Mean (± SD) or median (1^{st}-3^{rd} IQR)

Physical fitness

At the start of the trial the peak load and PeakVO_2 was not significantly different between the exercise and control-group. Peak load significantly increased in the exercise-group compared to the control-group (mean change peak load exercise-group 6.9 (3.4, 10.4) Watt; control-group 0.8 (−4.2, 5.8) Watt; $p = 0.047$). There was no significant difference between the increase of peakVO_2 in the exercise-group and that in the control-group. Within the exercise-group peakVO_2 increased (mean change peakVO_2 exercise-group 1.7 (0.4, 3.0) ml/kg/min, $p = 0.011$), the control-group did not increase their peakVO_2 (mean change peakVO_2 control-group 0.9 (−1.0, 2.8)ml/kg/min. Subgroup analyses showed that in ToF patients the exercise-group significantly increased its peak load compared to the control-group and significantly increased their peakVO_2 in the exercise-group, whereas in the Fontan patients no difference was observed.

Adverse events

No adverse events were reported during the exercise training sessions. One Fontan patient, in the exercise-group experienced a collapse one month after starting the training program. He collapsed while walking on the street. Further investigation did not clarify the reason for collapsing.

Outcome measurements

Magnetic resonance imaging

The MRI results are shown in Table 2a and 2b. The changes in MRI parameters, in left, right or single ventricle, were not statistically significant within groups and between the exercise-group and the control-group.

Echocardiography

Echocardiography results are shown in Table 3a and 3b. In ToF patients a small but statistically significant change was seen in the control-group in comparison to the exercise-group in MV peak A and TV peak E/A ratio ($p = 0.013$ and $p = 0.020$ respectively). Within group analysis showed a significantly decrease in MV peak A in the control-group ($p = 0.016$), but not in the exercise-group ($p = 0.100$). TV peak E/A ratio significantly increased in the control-group ($p = 0.017$) but not in the exercise-group ($p = 0.499$). None of the other inflow parameters changed in a statistically significant way. There were no relevant changes in pulmonary vein flow patterns.

None of the differences in change in echocardiographic parameters between the exercise-group and the control-group were significant in the Fontan patients.

Neurohormonal assessment

The results of neurohormonal assessment are shown in Table 4a and 4b. All baseline values were within normal (log transformed) range. There were no significant changes at follow-up assessment in either the exercise-group or the control-group.

DISCUSSION

Our study shows that no clinically relevant adverse remodeling occurs after aerobic dynamic exercise training in patients after surgical correction of tetralogy of Fallot or with a Fontan circulation. No adverse event directly linked to the exercise training program occurred in our study. To the best of our knowledge this is the first study demonstrating these favorable outcomes in congenital heart patients with important loading abnormalities of the heart.

The findings of our study put the perception of cardiac youth as being "at risk" during physical activity in another perspective[16]. This may be reassuring for patients, parents and caretakers, and may help them to encourage children and young adults with ConHD to engage in physical activities.

There are various good reasons to consider patients with ConHD candidates for exercise training. Repeated exercise reduces the long-term risk of acquired heart disease,

Table 2a: MRI results ToF patients

	Exercise-group (n = 26)			Control-group (n = 19)			Difference	*p*-value
	Before	After	Change before after	Before	After	Change before after	change exercise-control	
Left ventricle								
EDV_i (ml/m^2)	82 ± 13	81 ± 14	−1.2 (−3.9, 1.5)	86 ± 7	84 ± 11	−1.9 (−4.7, 0.9)	0.7 (−3.2, 4.6)	0.747
Ejection Fraction (%)	60 ± 8	59 ± 7	−0.01 (−0.03, 0.01)	61 ± 6	63 ± 8	0.01 (−0.01, 0.03)	−0.02 (−0.05, 0.01)	0.397
mass/EDV ratio	0.60 ± 0.10	0.61 ± 0.09	0.01 (−0.02, 0.04)	0.57 ± 0.08	0.57 ± 0.12	0.01 (−0.02, 0.04)	0 (−0.04, 0.04)	0.669
Right ventricle								
EDV_i (ml/m^2)	124 ± 32	122 ± 32	−2.2(−7.2, 2.8)	133 ± 36	132 ± 36	−0.2(−4.7, 4.3)	−2.0 (−8.7, 4.7)	0.588
SV_i effective (ml/m^2)	45 ± 10	41 ± 5	−4.0 (−10.8, 2.7)	45 ± 13	44 ± 10	−1.4 -10.8, 8.0)	−2.6 (−14.2, 9.0)	0.627
Ejection fraction effective (%)	35 ± 9	33 ± 8	−0.02 (−0.05, 0.01)	34 ± 11	33 ± 11	−0.001 (−0.04, 0.04)	−0.02 (−0.07, 0.03)	0.598
mass/EDV ratio	0.17 ± 0.05	0.17 ± 0.05	−0.005 (−0.02, 0.01)	0.15 ± 0.04	0.15 ± 0.04	−0.006 (−0.02, 0.01)	0.001 (−0.03, 0.03)	0.933
Pulmonary artery								
Pulmonary flow (ml)	75 ± 20	79 ± 21	3.5 (−4.1, 11.1)	81 ± 18	77 ± 16	−4.0 (−12.2, 4.2)	7.5 (−3.7, 18.7)	0.224
Fraction of regurgitation (%)	31 ± 14	32 ± 15	1.3 (−1.5, 4.1)	32 ± 15	36 ± 23	3.5 (−2.0, 9.0)	−2.2 (−8.4, 4.0)	0.592

EDV_i indexed end diastolic volume SV_i indexed stroke volume; mass/EDV mass-volume ratio. Values are shown as mean ± SD and changes are shown as mean (95% confidence interval). P-value relates to the between subjects comparisons, analyzed by two-way ANOVA.

Table 2b: MRI results Fontan patients

	Exercise-group (n = 21)			Control-group (n = 14)			Difference	*p*-value
	Before	After	Change before after	Before	After	Change before after	change exercise-control	
Single ventricle								
EDVi (ml/m^2)	89 (79 - 105)	89 (85 - 100)	−0.3 (−4.0, 3.4)	87 (75 - 116)	87 (77 - 101)	−2.2 (−7.4, 3.0)	1.9 (−4.5, 8.3)	0.545
Ejection Fraction (%)	52 ± 8	51 ± 9	−0.01 (−0.03, 0.01)	55 ± 9	57 ± 8	0.02 (−0.01, 0.05)	−0.03 (−0.07, 0.01)	0.144
mass/EDV ratio	0.59 (051 - 0.74)	0.63 (0.51 - 0.70)	−0.03 (−0.07, 0.01)	0.56 (0.41 - 0.60	0.49 (0.41 - 0.57)	0.02 (−0.04, 0.08)	−0.05 (−0.1, 0.03)	0.704

EDV_i indexed end diastolic volume; mass/EDV mass- volume ratio. Values are shown as mean ± SD and changes are shown as mean (95% confidence interval). P-value relates to the between subjects comparisons, analyzed by two-way ANOVA.

Table 3a: Echocardiography results ToF patients

	Exercise-group (n = 27)			Control-group (n = 20)			Difference	*p*-value
	Before	After	Change before after	Before	After	Change before after	change exercise-control	
LV Wall stress (g/cm^2)	64.1 ± 37.4	58.9 ± 22.3	5.2 (−8.7, 19.1)	69.5 ± 22.4	67.4 ± 25.1	2.2 (−7.3, 11.7)	3.0 (−13.8, 19.8)	0.772
MAPSE (mm)	17.4 ± 3.0	16.3 ± 3.2	−1.12 (−2.4, 0.1)	14.3 ± 1.9	15.2 ± 2.5	0.88 (−0.001, 1.8)	−2.0 (−3.5, −0.5)	0.074
TAPSE (mm)	16.6 (15.0 - 18.3)	16.3 (12.5 - 19.7)	−0.39 (−1.4, 0.6)	16.5 (15.4 - 17.7)	15.8 (14.3 - 18.5)	0.29(−1.5, 2.0)	−0.7 (−2.7, 1.3)	0.497
MV peak E (m/s)	0.99 ± 0.20	0.98 ± 0.22	−0.02(−0.10, 0.06)	1.02 ± 0.21	0.91 ± 0.18	−0.11(−0.19, −0.04)	0.09(−0.02, 0.20)	0.122
MV peak A (m/s)	0.48 ± 0.09	0.52 ± 0.17	0.04(−0.02, 0.10)	0.58 ± 0.17	0.48 ± 0.13	−0.10(−0.18, −0.02)	0.14(0.04, 0.24)	0.013
MV deceleration time E (ms)	174 (142 - 218)	158 (134 - 207)	−18.08(−41.5, 5.4)	190 (155 - 262)	171 (132 - 263)	−10.01(−50.8, 30.8)	−8.1(−55.1, 39.0)	0.748
MV peak E/A ratio	2.1 ± 0.6	2.0 ± 0.6	−0.11(−0.32, 0.10)	1.9 ± 0.5	2.0 ± 0.5	0.14(−0.19, 0.47)	−0.25(−0.64, 0.14	0.241
TV peak E (m/s)	0.73 ± 0.15	0.72 ± 0.10	−0.02(−0.07, 0.03)	0.69 ± 0.10	0.68 ± 0.12	−0.01(−0.06, 0.04)	−0.01(−0.08, 0.06)	0.877
TV peak A (m/s)	0.44 ± 0.14	0.44 ± 0.09	−0.01(−0.06, 0.04)	0.47 ± 0.11	0.38 ± 0.10	−0.08(−0.14, −0.01)	0.07(−0.01, 0.15)	0.061
TV deceleration time E (ms)	178 (166 - 240)	157 (143 - 226)	13,9(−18.5, 46.3)	164 (146 - 212)	171 (122 - 230)	−7.7(−27.7, 12.3)	21.6(−16.5, 59.7)	0.326
TV peak E/A ratio	1.59 (1.39 - 1.95)	1.67 (1.34 - 1.88)	−0.08(−0.29, 0.13)	1.52 (1.17 - 1.70)	1.78 (1.37 - 2.11)	0.33(0.09, 0.57)	−0.41(−0.73, −0.09)	0.020
TR (m/s)	0.04 (0.03 - 1.96)	0.04 (0.03 - 2.30)	0.04(−0.03, 0.11)	1.77 (0.03 - 2.18)	0.67 (0.03 - 2.32)	−0.04(−0.23, 0.15)	0.08(−0.12, 0.28)	0.511
RUPV peak S (m/s)	0.51 ± 0.19	0.52 ± 0.22	0.02(−0.04, 0.08)	0.50 ± 0.19	0.53 ± 0.16	0.03(−0.05, 0.11)	−0.01(−0.11, 0.09)	0.920
RUPV peak D (m/s)	0.72 ± 0.17	0.73 ± 0.18	0.02(−0.06, 0.10)	0.74 ± 0.18	0.68 ± 0.19	−0.06(−0.15, 0.03)	0.08(−0.04, 0.20)	0.253
RUPV S/D ratio	0.76 (0.59 - 0.85)	0.64 (0.54 - 0.86)	0.06(−0.08, 0.20)	0.64 (0.52 - 0.76)	0.67 (0.61 - 0.96)	0.14(−0.08, 0.36)	−0.08(−0.34, 0.18)	0.549
Aorta ascendens peak (m/s)	0.92 ± 0.16	0.95 ± 0.19	0.03(−0.05, 0.11)	1.02 ± 0.22	0.93 ± 0.11	−0.09(−0.17, −0.02)	0.12(0.01, 0.23)	0.112
Pulmonary peak systole (m/s)	1.67 ± 0.54	1.70 ± 0.44	0.02(−0.20, 0.24)	1.72 ± 0.46	1.71 ± 0.45	−0.005(−0.18, 0.17)	0.03(−0.25, 0.30)	0.858

LV left ventricle; MAPSE: mitral annular plane systolic excursion; TAPSE: tricuspid annular plane systolic excursion; MV mitral valve; peak E velocity of the transmitral/ transtricuspid E wave; peak A velocity of the transmitral/ transtricuspid A wave; TV tricuspid valve; RUPV: right upper pulmonary vein; peak S velocity of the systolic wave; peak D velocity of the diastolic wave. Values are shown as mean ± SD or median and interquartile range and changes are shown as mean (95% confidence interval). P-value relates to the between subjects comparisons, analyzed by two-way ANOVA.

Table 3b: Echocardiography results Fontan patients

	Exercise-group (n = 24)			Control-group (n = 15)			Difference	*p*-value
	Before	After	Change before after	Before	After	Change before after	change exercise-control	
Dominant APSE (mm)	11.6 ± 2.7	11.2 ± 2.6	−0.34(−0.08, 0.20)	11.9 ± 2.3	11.8 ± 2.4	−0.11 (−1.24, 1.02)	−0.23 (−2.06, 1.60)	0.835
Dominant AV-valve peak E (m/s)	0.70 (0.59 - 0.86)	0.77 (0.61 - 1.02)	0.08(−0.004, 0.164)	0.65 (0.58 - 0.80)	0.69 (0.57 - 0.85)	0.06 (0.004, 0.116)	0.02 (−0.08, 0.12)	0.699
Dominant AV-valve peak A (m/s)	0.53 ± 0.15	0.52 ± 0.20	−0,002-0.106, 0.102)	0.51 ± 0.14	0.57 ± 0.19	0.060 (−0.046, 0.166)	−0.062 (−0.211, 0.087)	0.471
Dominant AV-valve deceleration time E (ms)	192 (155 - 268)	170 (133 - 226)	−37.7(−58.6, −16.8)	184 (154 - 279)	166 (105 - 203)	−26.1 (−59.3, 7.1)	−11.6 (−50.9, 27.7)	0.566
Dominant AV-valve peak E/A ratio	1.42 (1.12 - 1.83)	1.57 (1.31 - 2.16)	0.17(−0.05, 0.39)	1.40 (1.13 - 1.73)	1.36 (1.05 - 1.67)	−0.06 (−0.27, 0.15)	0.23 (−0.08, 0.54)	0.190
RUPV peak S (m/s)	0.40 ± 0.13	0.38 ± 0.15	−0.02(−0.10, 0.06)	0.46 ± 0.15	0.43 ± 0.08	−0.03 (−0.11, 0.05)	0.01 (−0.10, 0.12)	0.941
RUPV peak D (m/s)	0.63 ± 0.15	0.57 ± 0.15	−0.06(−0.14, 0.02)	0.58 ± 0.15	0.62 ± 0.12	0.03 (−0.01, 0.07)	−0.09 (−0.18, −0.004)	0.081
RUPV velocity S/D ratio	0.67 ± 0.24	0.68 ± 0.21	0.02(−0.07, 0.11)	0.80 ± 0.25	0.72 ± 0.19	−0.08 (−0.18, 0.02)	0.10 (−0.04, 0.24)	0.233
Aorta ascendens peak (m/s)	0.95 (0.81 - 1.16)	0.99 (0.85 - 1.08)	0.04(−0.03, 0.11)	1.03 (0.90 - 1.14)	0.96 (0.85 - 1.11)	0.02 (−0.05, 0.09)	0.02 (−0.08, 0.12)	0.761

APSE annular plane systolic excursion; AV atrioventricular valve; peak E velocity of the dominant AV-valve E wave; peak A velocity of the dominant AV-valve A wave; RUPV: right upper pulmonary vein; peak S velocity of the systolic wave; peak D velocity of the diastolic wave. Values are shown as mean ± SD or median and interquartile range and changes are shown as mean (95% confidence interval). P-value relates to the between subjects comparisons, analyzed by two-way ANOVA.

Table 4a: Results of neurohormonal assessment ToF patients

	Exercise-group (n = 24)			Control-group (n = 20)			Difference		*p*-value
	Before	After	Change before after	Before	After	Change before after	change exercise-control		Log reference
NT-proBNP (log pmol/L)	0.93 ± 0.37	0.86 ± 0.30	−0.07 (−0.16, 0.02)	1.00 ± 0.33	0.86 ± 0.30	−0.06 (−0.14, 0.02)	−0.01 (−0.13, 0.11)	0.872	<1.18
Renin (log µ/ml)	1.40 ± 0.29	1.39 ± 0.30	−0.01 (−0.14, 0.12)	1.40 ± 0.26	1.44 ± 0.20	0.05 (−0.06, 0.16)	−0.06 (−0.23, 0.11)	0.529	0.70 - 1.78
Adrenalin (log pg/ml)	1.28 (0.70 - 1.65)	1.20 (0 - 1.58)	−0.28 (−0.63, 0.07)	1.22 (0.86 - 1.43)	1.15 (0 - 1.30)	−0.14 (−0.38, 0.10)	−0.14 (−0.56, 0.28)	0.542	<2.08
Noradrenalin (log pg/ml)	2.31 ± 0.20	2.32 ± 0.21	0.01 (−0.09, 0.11)	2.25 ± 0.21	2.26 ± 0.30	0.01 (−0.10, 0.12)	0 (−0.15, 0.15)	0.919	2 - 2.78
Aldosterone (log pg/ml)	1.84 ± 0.280	1.89 ± 0.32	0.04 (−0.10, 0.18)	1.93 ± 0.26	1.87 ± 0.22	−0.06 (−0.19, 0.07)	0.10 (−0.09, 0.29)	0.301	1.40 – 2.40
Dopamine (log pg/ml)	0.83 (0.36 - 1.55)	0.70 (0 - 1.73)	−0.18 (−0.53, 0.17)	0.83 (0 - 1.22)	1.25 (0 - 1.60)	0.24 (−0.08, 0.56)	−0.42 (−0.90, 0.06)	0.124	<1.70

All values are log transformed. NT-proBNP: N-terminal pro-brain natriuretic peptide. Values are shown as mean ± SD or median and interquartile range and changes are shown as mean (95% confidence interval). P-value relates to the between subjects comparisons, analyzed by two-way ANOVA.

Table 4b: Results of neurohormonal assessment Fontan patients

	Exercise-group (n = 23)			Control-group (n = 15)			Difference		*p*-value
	Before	After	Change before after	Before	After	Change before after	change exercise-control		Log reference
NT-proBNP (log pmol/L)	1.18 ± 0.29	1.16 ± 0.35	−0.02 (−0.07, 0.03)	0.96 ± 0.34	0.94 ± 0.35	−0.02 (−0.10, 0.06)	0 (−0.09, 0.09)	0.982	<1.18
Renin (log µ/ml)	1.51 ± 0.33	1.49 ± 0.29	−0.02 (−0.11, 0.07)	1.60 ± 0.22	1.46 ± 0.19	−0.14 (−0.27, −0.01)	0.12 (−0.04, 0.28)	0.175	0.70 - 1.78
Adrenalin (log pg/ml)	1.46(0.78 - 1.66)	1.18 (0.93 - 1.55)	−0.09 (−0.34, 0.15)	1.32 (081 - 1.76)	1.21 (0.36 - 1.75)	−0.08 (−0.40, 0.24)	−0.01 (−0.41, 0.39)	0.962	<2.08
Noradrenalin (log pg/ml)	2.50 ± 0.16	2.48 ± 0.20	−0.02 (−0.11, 0.07)	2.56 ± 0.01	2.48 ± 0.23	−0.08 (−0.19, 0.03)	0.06 (−0.08, 0.20)	0.402	2 - 2.78
Aldosterone (log pg/ml)	1.71 ± 0.26	1.62 ± 0.35	−0.03 (−0.16, 0.10)	1.86 ± 0.38	1.62 ± 0.35	−0.24 (−0.43, −0.05)	0.21 (−0.02, 0.44)	0.099	1.40 – 2.40
Dopamine (log pg/ml)	0(0 - 0.81)	0(0 - 0.60)	−0.04 (−0.36, 0.28)	0.30 (0 - 0.80)	0 (0 - 1.22)	0.18 (−0.07, 0.43)	−0.22 (−0.62, 0.18)	0.409	<1.70

All values are log transformed. NT-proBNP: N-terminal pro-brain natriuretic peptide. Values are shown as mean ± SD or median and interquartile range and changes are shown as mean (95% confidence interval). P-value relates to the between subjects comparisons, analyzed by two-way ANOVA.

improves fitness and increases quality of life[17]. Beneficial effects of exercise training have been shown with regard to cardiac hypertrophy, the contraction and relaxation machinery, and renewal and regeneration capability[18]. In addition exercise training has been associated with favorable changes in the inflammatory balance[19]. Remarkably, these effects have hardly been studied in congenital heart disease. In fact, only small studies in heterogeneous patient groups with congenital heart disease have been done[9]. A total of 621 patients with congenital heart disease who performed in exercise training have been reported in 31 studies so far. Dynamic exercise training 3 times a week for 12 weeks was used most commonly[9]. In 72% of the studies a significant positive change for outcome measures, mostly PeakVO_2, was assessed. It is highly remarkable that hardly any of these studies assessed cardiac effects[9].

Exercise related cardiac remodeling

In healthy adults as well as in children, physiological remodeling, with increased LV diameters and wall thickness, has been shown in response to dynamic aerobic exercise training[7, 8, 20]. Exercise training results in enhanced systolic contractility and improved diastolic filling, resulting from improved myocardial relaxation, better compliance, decrease in filling pressures and increased contribution of atrial contraction. Subsequently during exercise stroke volume increases and cardiac output may increase significantly[7, 21].

In adults with acquired heart disease exercise training with duration as short as 8 weeks has shown to results in favorable cardiac remodeling. Aerobic endurance training partially reversed adverse left ventricular remodeling and improved left ventricular ejection fraction[22]. Alves et al. showed significantly improvement of LV diastolic function in 98 patients with different degrees of reduced LV ejection fraction[20]. However, changes in diastolic function have not been a general finding in response exercise training in patients with heart failure with preserved ejection fraction[23]. Although changes in the left ventricle are the main focus in exercise training studies in acquired heart disease, and the right ventricle is of interest in most of the research in ConHD population, it is known that changes due to exercise in the left ventricle are similar in the right ventricle[7].

Our study in ConHD patients showed no clinically relevant changes in systolic function, as stroke volume, ejection fraction, echo measures of longitudinal ventricular chamber motion and dimensions did not change in both ToF and Fontan patients after exercise training.

Diastolic parameters did not change in a clinically relevant way in our study. Although there were some isolated minor changes in inflow parameters, there was no consistent pattern of changes in both inflow parameters as well as upstream changes in venous flow profiles, indicating a lack of true diastolic function changes. The lack of adverse changes in diastolic function is important, since diastolic dysfunction may precede sys-

tolic dysfunction[24]. In our study this early marker of cardiac dysfunction was unaffected by exercise training.

In contrast to the large body of evidence demonstrating cardiac effects of exercise training in adults with various types of heart disease, few studies have been done in patients with congenital heart disease. In a small study by Cordina et al cardiac filling, stroke volume and cardiac output were assessed with MRI in 4 adult Fontan patients who had participated in a 20 week resistance training program[25]. MRI measurements were obtained while the patient was on continuous positive airway pressure (CPAP), which negatively affects intrathoracic pressures and reduces cardiac filling. Nevertheless, significant improvements in cardiac function were shown after the training program. Sklansky et al measured the influence of an 8 week aerobic training program in 11 children with corrected tetralogy of Fallot by echocardiography. In their study, LV end-diastolic dimension as well as LV posterior wall thickness did not change significantly[26]. The current study for the first time shows in a randomized control trial that exercise training in ConHD patients does not lead to clinically relevant adverse remodeling of biventricular or single ventricular hearts. Adverse events were not always reported in previous exercise studies with patients with ConHD. Only 9 out of 31 exercise training programs with ConHD patients reported possible adverse events. In these 9, in generally small heterogeneous studies, no adverse events were reported, which strengthens our findings[9].

Exercise related changes in neurohormonal assessment

NT-proBNP rises during exercise in response to excessive atrial and ventricular wall stress[27]. Increased NT-pro-BNP and other neurohormonal markers, indicating adrenergic and RAAS activation, have been associated with impaired long-term prognosis in congenital heart disease[28].

In heart failure patients a training program resulted in significant decrease of NT-proBNP (1370 ± 234 to 929 ± 206 ng/L)as well as noradrenaline (607 ± 55 to 447 ± 39)[29]. However, the baseline measurements were much higher than the measurements in our study. In our patients levels of NT-proBNP, renine, adrenaline, noradrenaline, aldosterone and dopamine were within normal range or slightly increased at baseline and did not change significantly after the exercise program. This fits the imaging observations, demonstrating no signs of adverse remodeling.

Signs of neurohormonal activation have hardly been studied after exercise training in congenital heart disease. Previous studies in adult Fontan patients following a 10 week aerobic exercise training program also noted an absence of change in the level of NT-proBNP[30, 31].

This may relate to differences in pathophysiology between acquired and congenital heart disease, or to differences in disease state during which exercise training was per-

formed. Our patients were in relatively good clinical state, without signs of heart failure. This may explain the limited favorable effect that we noted, although the level of change of peak VO2 and peak workload are in accordance to those observed in acquired heart disease and in other studies in congenital heart disease[9, 22].

Effect of exercise training type

The generally good clinical state of our patients is in contrast to those in exercise training studies in acquired heart disease heart failure[20, 32, 33]. In the latter patient groups, muscle wasting is commonly observed. Part of the effect of exercise training in these groups is explained by improved function of skeletal muscle, including breathing musculature[34]. Because of these observation, other types of exercise than dynamic aerobic exercise have been explored, particularly resistance training and high intensity interval training. Results of resistance training are equivocal[22]. A small study in Fontan patients has demonstrated that resistance training improved muscle mass and strength[25]. Aerobic interval training seems more effective than continuous training for stable patients with heart failure and reduced ejection fraction[22]. This has not been tested in larger studies in patients with ConHD. Our training design is generally in line with current physical activity recommendations for patients with ConHD as described by Budts et al.[35]. In accordance with their general and non-specific advice to individualize training levels training intensity in our study was set at 60 - 70% of the individual heart rate reserve. By using heart rate reserve we personalized the training program yet ensuring that each individual reached the same intensity of training.

Limitations

Although our sample size is small compared to the intervention studies in adults with acquired heart disease, it is quite large in its field. This study alone included a number of patients equaling 15 % of all patients that have been reported before in 31 studies in this field. Furthermore, most of these previous studies included patients with a variety of congenital cardiac conditions[9]. Not all of our eligible patients were willing to undergo MRI studies or blood testing and not all patients had a favorable acoustic window. We have measured the effects of exercise training on cardiac remodeling directly after the intervention period. To assess long-term effects a second follow-up assessment would have been needed. We unfortunately were unable to include such a subsequent follow-up visit in our trial. We have chosen to perform an exercise study with an aerobic training design. We did not investigate the effects of resistance training or a high intensity exercise program. Nevertheless, this study finds strength in the fact that two well defined patient groups participated; the research was carried out and supervised in a prospective way and a well supervised training program was used.

Clinical relevance

ToF and Fontan patients are among those with ConHD with the highest risk for late development of heart failure[1]. They may be considered the patients to benefit the most from potential positive effects of exercise training[9]. Our results provide evidence for the absence of adverse remodeling in these patients. This type of data has been lacking so far and may contribute to improved quality of current recommendations for physical activity and exercise training in patients with congenital heart disease. Further studies are required to assess the long-term effects of exercise training programs in congenital heart disease and the effects of different type of exercise training in these patients.

Conclusions

We demonstrated that no clinically relevant adverse cardiac remodeling occurred after 12 weeks exercise training in children and young adult patients with either a corrected tetralogy of Fallot or a Fontan circulation.

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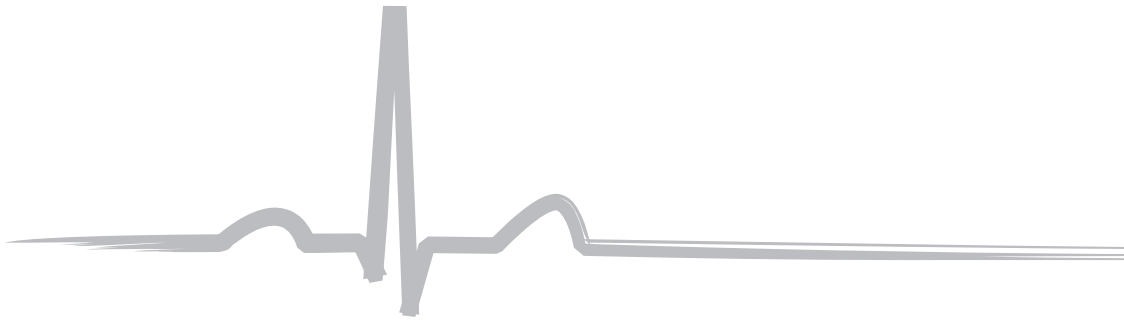
REFERENCES

1. Norozi K, Wessel A, Alpers V, Arnhold JO, Geyer S, Zoege M, Buchhorn R. Incidence and risk distribution of heart failure in adolescents and adults with congenital heart disease after cardiac surgery. *Am J Cardiol*. 2006;97:1238-1243
2. Hirth A, Reybrouck T, Bjarnason-Wehrens B, Lawrenz W, Hoffmann A. Recommendations for participation in competitive and leisure sports in patients with congenital heart disease: A consensus document. *Eur J Cardiovasc Prev Rehabil*. 2006;13:293-299
3. Takken T, Giardini A, Reybrouck T, Gewillig M, Hovels-Gurich HH, Longmuir PE, McCrindle BW, Paridon SM, Hager A. Recommendations for physical activity, recreation sport, and exercise training in paediatric patients with congenital heart disease: A report from the exercise, basic & translational research section of the european association of cardiovascular prevention and rehabilitation, the european congenital heart and lung exercise group, and the association for european paediatric cardiology. *Eur J Prev Cardiol*. 2012;19:1034-1065
4. Reybrouck T, Mertens L. Physical performance and physical activity in grown-up congenital heart disease. *Eur J Cardiovasc Prev Rehabil*. 2005;12:498-502
5. Longmuir PE, McCrindle BW. Physical activity restrictions for children after the fontan operation: Disagreement between parent, cardiologist, and medical record reports. *Am Heart J*. 2009;157: 853-859
6. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: A consensus paper from an international forum on cardiac remodeling. Behalf of an international forum on cardiac remodeling. *J Am Coll Cardiol*. 2000;35:569-582
7. La Gerche A, Taylor AJ, Prior DL. Athlete's heart: The potential for multimodality imaging to address the critical remaining questions. *JACC Cardiovasc Imaging*. 2009;2:350-363
8. Sharma S, Maron BJ, Whyte G, Firoozi S, Elliott PM, McKenna WJ. Physiologic limits of left ventricular hypertrophy in elite junior athletes: Relevance to differential diagnosis of athlete's heart and hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2002;40:1431-1436
9. Duppen N, Takken T, Hopman MT, ten Harkel AD, Dulfer K, Utens EM, Helbing WA. Systematic review of the effects of physical exercise training programmes in children and young adults with congenital heart disease. *Int J Cardiol*. 2013;168:1779-1787
10. Schulz KF, Altman DG, Moher D, Group C. Consort 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332
11. Armstrong N, van Mechelen W. Aerobic fitness. *Paediatric exercise science and medicine*. Oxford: Oxford University Press; 2008:97-108.
12. Robbers-Visser D, Luijnenburg SE, van den Berg J, Roos-Hesselink JW, Strengers JL, Kapusta L, Moelker A, Helbing WA. Safety and observer variability of cardiac magnetic resonance imaging combined with low-dose dobutamine stress-testing in patients with complex congenital heart disease. *Int J Cardiol*. 2011;147:214-218
13. Lai WW, Geva T, Shirali GS, Frommelt PC, Humes RA, Brook MM, Pignatelli RH, Rychik J, Task Force of the Pediatric Council of the American Society of E, Pediatric Council of the American Society of E. Guidelines and standards for performance of a pediatric echocardiogram: A report from the task force of the pediatric council of the american society of echocardiography. *J Am Soc Echocardiogr*. 2006;19:1413-1430
14. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W, American Society of Echocardiography's N, Standards C, Task Force on Chamber Q, American College of Cardiol-

ogy Echocardiography C, American Heart A, European Association of Echocardiography ESoC. Recommendations for chamber quantification. *Eur J Echocardiogr*. 2006;7:79-108
15. Mizuno R, Fujimoto S, Saito Y, Okamoto Y. Detection of latent anthracycline-induced cardiotoxicity using left ventricular end-systolic wall stress-velocity of circumferential fiber-shortening relationship. *Heart Vessels*. 2014;29:384-389
16. Moola F, Fusco C, Kirsh JA. The perceptions of caregivers toward physical activity and health in youth with congenital heart disease. *Qual Health Res*. 2011;21:278-291
17. Swift DL, Lavie CJ, Johannsen NM, Arena R, Earnest CP, O'Keefe JH, Milani RV, Blair SN, Church TS. Physical activity, cardiorespiratory fitness, and exercise training in primary and secondary coronary prevention. *Circ J*. 2013;77:281-292
18. Ellison GM, Waring CD, Vicinanza C, Torella D. Physiological cardiac remodelling in response to endurance exercise training: Cellular and molecular mechanisms. *Heart*. 2012;98:5-10
19. Lavie CJ, Church TS, Milani RV, Earnest CP. Impact of physical activity, cardiorespiratory fitness, and exercise training on markers of inflammation. *J Cardiopulm Rehabil Prev*. 2011;31:137-145
20. Alves AJ, Ribeiro F, Goldhammer E, Rivlin Y, Rosenschein U, Viana JL, Duarte JA, Sagiv M, Oliveira J. Exercise training improves diastolic function in heart failure patients. *Med Sci Sports Exerc*. 2012; 44:776-785
21. Baggish AL, Wood MJ. Athlete's heart and cardiovascular care of the athlete: Scientific and clinical update. *Circulation*. 2011;123:2723-2735
22. Haykowsky MJ, Liang Y, Pechter D, Jones LW, McAlister FA, Clark AM. A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: The benefit depends on the type of training performed. *J Am Coll Cardiol*. 2007;49:2329-2336
23. Taylor RS, Davies EJ, Dalal HM, Davis R, Doherty P, Cooper C, Holland DJ, Jolly K, Smart NA. Effects of exercise training for heart failure with preserved ejection fraction: A systematic review and meta-analysis of comparative studies. *Int J Cardiol*. 2012;162:6-13
24. van den Berg J, Wielopolski PA, Meijboom FJ, Witsenburg M, Bogers AJ, Pattynama PM, Helbing WA. Diastolic function in repaired tetralogy of fallot at rest and during stress: Assessment with mr imaging. *Radiology*. 2007;243:212-219
25. Cordina RL, O'Meagher S, Karmali A, Rae CL, Liess C, Kemp GJ, Puranik R, Singh N, Celermajer DS. Resistance training improves cardiac output, exercise capacity and tolerance to positive airway pressure in fontan physiology. *Int J Cardiol*. 2013;168:780-788
26. Sklansky MS, Pivarnik JM, O'Brian Smith E, Morris J, Bricker JT. Exercise training hemodynamics and the prevalence of arrhythmia's in children following tetralogy of fallot repair. *Pediatric Exercise Science*. 1994;6:188-200
27. Hager A, Christov F, Hess J. Increase in n-terminus-pro-b-type natriuretic peptide during exercise of patients with univentricular heart after a total cavopulmonary connection. *Pediatr Cardiol*. 2012;33:764-769
28. Bolger AP, Sharma R, Li W, Leenarts M, Kalra PR, Kemp M, Coats AJ, Anker SD, Gatzoulis MA. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. *Circulation*. 2002;106:92-99
29. Passino C, Severino S, Poletti R, Piepoli MF, Mammini C, Clerico A, Gabutti A, Nassi G, Emdin M. Aerobic training decreases b-type natriuretic peptide expression and adrenergic activation in patients with heart failure. *J Am Coll Cardiol*. 2006;47:1835-1839
30. Winter MM, van der Bom T, de Vries LC, Balducci A, Bouma BJ, Pieper PG, van Dijk AP, van der Plas MN, Picchio FM, Mulder BJ. Exercise training improves exercise capacity in adult patients with a systemic right ventricle: A randomized clinical trial. *Eur Heart J*. 2012;33:1378-1385

31. Martinez-Quintana E, Miranda-Calderin G, Ugarte-Lopetegui A, Rodriguez-Gonzalez F. Rehabilitation program in adult congenital heart disease patients with pulmonary hypertension. *Congenit Heart Dis*. 2010;5:44-50
32. Spruit MA, Eterman RM, Hellwig VA, Janssen PP, Wouters EF, Uszko-Lencer NH. Effects of moderate-to-high intensity resistance training in patients with chronic heart failure. *Heart*. 2009;95: 1399-1408
33. Cantinotti M, Lopez L. Nomograms for blood flow and tissue doppler velocities to evaluate diastolic function in children: A critical review. *J Am Soc Echocardiogr*. 2013;26:126-141
34. Conraads VM, Van Craenenbroeck EM, De Maeyer C, Van Berendoncks AM, Beckers PJ, Vrints CJ. Unraveling new mechanisms of exercise intolerance in chronic heart failure: Role of exercise training. *Heart Fail Rev*. 2013;18:65-77
35. Budts W, Borjesson M, Chessa M, van Buuren F, Trigo Trindade P, Corrado D, Heidbuchel H, Webb G, Holm J, Papadakis M. Physical activity in adolescents and adults with congenital heart defects: Individualized exercise prescription. *Eur Heart J*. 2013;34:3669-3674



Chapter 6

Regional ventricular performance and exercise training in children and young adults after repair of tetralogy of Fallot: a randomized controlled trial.

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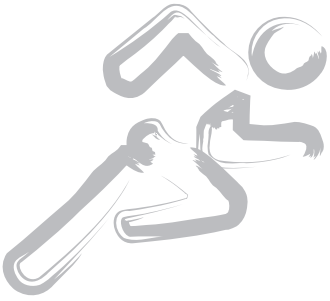

ABSTRACT

Background: Public-health guidelines recommend patients with congenital heart disease (ConHD) to exercise. Studies have shown that ConHD patients can improve physical exercise capacity. The effect of training on regional ventricular performance has hardly been studied. We performed a pilot study to assess if an exercise training program would result in adverse changes of regional ventricular performance in patients with corrected tetralogy of Fallot (ToF).

Methods and Results: Multi-center prospective randomized controlled pilot study in ToF patients aged 10-25 years. A 12-week standardized aerobic dynamic exercise training program (three 1-hour sessions per week) was used. Pre- and post-training cardiopulmonary exercise tests, magnetic resonance imaging and echocardiography, including tissue-Doppler imaging (TDI), were performed. Patients were randomized to the exercise-group (n = 28) or control-group (n = 20). One patient in the exercise-group dropped out. Change in TDI parameters was similar in the exercise-group and control-group (change in right ventricle free wall peak velocity E' exercise-group 0.8 ± 2.6 cm/s, control-group 0.9 ± 4.1; peak velocity A' exercise-group 0.4 ± 2.4 m/s, control-group 4.6 ± 18.1 cm/s).

Conclusions: This randomized controlled pilot study provides preliminary data suggesting that regional ventricular performance is well maintained during 3 - month aerobic dynamic exercise training in children and young adults with repaired ToF. This information might help patients adhere to current public-health guidelines.

INTRODUCTION

Current public-health guidelines recommend patients with congenital heart disease (ConHD) to engage in exercise[1]. These guidelines are partly based on reports in patients with acquired heart disease and heart failure. These reports have shown that repeated exercise reduces the long-term risk associated with acquired heart disease and heart failure, improves fitness, and increases quality of life[2]. However, many patients with ConHD do not exercise. The reluctance to exercise in these patients may in part result from fear of a negative effect of exercise on their heart[3-6]. Of all patients with ConHD, patients with tetralogy of Fallot (ToF) are amongst those with a high chance of developing heart failure[7]. As such, they may be considered to benefit most from exercise training.

Exercise training in patients with ConHD has been the subject of several studies, generally in small mixed populations[8]. Although these studies have shown that patients with ConHD can improve their physical exercise capacity, the effect of exercise training on ventricular performance has hardly been studied[8].

In contrast, the ventricular response to acute stress (physical or pharmacological) has been studied extensively in ToF patients demonstrating highly abnormal changes for parameters of global ventricular function[9]. Furthermore, right ventricular regional functional abnormalities have been shown to occur during acute exercise in these patients[5]. Chronic loading abnormalities have been associated with abnormal regional function at rest, abnormal mass/volume ratio and signs of (areas of) fibrosis in many types of ConHD. These factors may contribute to abnormal ventricular wall stress that has been associated with adverse myocardial remodeling. Evidence from animal models of ConHD is limited, but abnormal right ventricular loading conditions have been associated with loading condition dependent abnormalities in voluntary exercise[10].

Conventional echocardiographic parameters are widely used for the assessment of global ventricular myocardial function. In addition, regional ventricular myocardial function can be assessed with tissue Doppler imaging (TDI)[11, 12]. Regional ventricular performance changes have been recognized as sensitive markers of deterioration of ventricular function[13].

This paper is the first to report a pilot study on regional cardiac changes after an exercise training program in a population of ConHD. Considering the knowledge gap with regard to the cardiac effects of exercise training, a first step to increase our knowledge would be to demonstrate a lack of adverse effects on the ventricles in response to a common and widely used type of exercise training in patients with highly abnormal loading conditions of the heart, such as in ToF patients.

For this purpose we performed a randomized controlled pilot study. The hypothesis was that exercise training would not lead to deterioration of regional ventricular performance. We performed a pilot study to assess if a 12-week standardized aerobic dynamic

exercise training program would result in adverse changes in regional ventricular performance in ToF patients.

METHODS

This study is a part of a broader initiative to evaluate the effects of exercise training in ConHD.

Trial design

This study consisted of a multi-center prospective randomized controlled trial and was conducted in 5 tertiary referral centers for ConHD in the Netherlands (Amsterdam, Leiden, Rotterdam, Nijmegen, and Utrecht). The study was designed according to Consolidated Standards of Reporting Trials (CONSORT) guidelines[14]. The trial was registered at www.trialregister.nl (identification number NTR2731).

Participants

Eligible participants were all children and young adults (aged 10 – 25 years) with corrected ToF. Surgical correction of ToF had to be performed through a transatrial-transpulmonary approach. Patients with ventricular outflow tract obstruction with a Doppler derived peak greater than 60 mmHg were excluded, as were all patients that were physically or mentally unable to execute a training program. Those patients, who were identified by their own physician and included patients with a hemiplegia or a mental retardation who were unable to follow instructions, needed to adhere to the physical exercise training sessions.

Patients were identified through the local databases of the participating hospitals. The study complied with the Declaration of Helsinki. Institutional Ethics Committees of all participating centers approved the research protocol. All participants (or their parents if required) signed a written informed consent.

Intervention

Randomization of participants was performed by an independent blinded researcher with a 2:1 allocation ratio to either the exercise training program (exercise-group) or to continue normal daily life (control-group). Stratification was done based on gender, congenital heart defect, and age group (10 – 12 years, 12 – 15 years, 15 – 18 years and 18 – 25 years).

The exercise-group was enrolled in a 12-week standardized aerobic dynamic exercise training program at submaximal levels, with three 1-hour sessions per week. The training hour was divided into 40 minutes of aerobic dynamic exercise training (e.g. cycling) and

10 minutes of both warming up and cooling down. Participants were given a heart rate monitor (SR400, Polar Electro the Netherlands BV, the Netherlands) to help them train within the predetermined submaximal heart rate range. This range was set at 60 to 70% of the heart rate reserve, which was determined by a cardiopulmonary exercise test (CPET) prior to the training program.

The training program was supervised by a local physiotherapist. The physiotherapist monitored the heart rate range during sessions. An attendance list was kept to monitor adherence. A single researcher visited the participating physiotherapists prior to the program to ensure that it was executed in a similar way for all participants.

Cardio-respiratory fitness

Peak workload and peak oxygen uptake (peakVO_2) were assessed by CPET. The same locally available ergometer and gas analyzers were used per patient before and after the 3-month period. A modified Bruce exercise protocol was used, with settings adjusted to age, height, and gender. All participants were encouraged to continue until exhaustion, which was defined as the inability to maintain 65 rotations per minute. The test was marked successful if a respiratory exchange ratio (RER) of at least 1.0 was attained during the maximal test phase, according to common guidelines[15].

Echocardiography

All participants underwent transthoracic echocardiography. This was performed by experienced technicians and supervised by the research team. Images were obtained according to a strict protocol, which was in agreement with common guidelines[11]. An appropriate transducer was used, based on age and weight. Each study was performed at rest on locally available machines. Five subsequent heart beats were recorded. Images were analyzed using offline EchoPac (GE, Horten, Norway), Xcelera and Qlab (Andover, USA) software.

Conventional echocardiography parameters

All reported conventional parameters were measured 3 times and averaged The following parameters were determined at baseline: ratio of maximum and minimum IVC dimensions; ratio of liver vein peak S and peak D flow; interventricular septum dimension in diastole (IVSd); left ventricular posterior wall dimension in diastole (LVPWd); maximum peak flow velocities in the great arteries and across the atrioventricular valves (Doppler E and A); peak systolic (S) and peak diastolic (D) flow in the superior vena cava (SVC); and maximal mitral and tricuspid annular plane systolic excursions (MAPSE and TAPSE, respectively)[11].

Tissue Doppler imaging

All reported TDI parameters were measured 3 times and averaged. TDI parameters were obtained in the apical four-chamber view (AP4CH). Longitudinal myocardial velocity curves were obtained from the basal parts of the interventricular septum (IVS) and both the left ventricle and right ventricle or dominant free walls. Peak systolic myocardial velocity (S'), peak early diastolic myocardial velocity (E'), peak late diastolic myocardial velocity (A'), and time to peak systolic myocardial velocity were measured. Isovolumic acceleration was assessed by tracing the slope. In addition to the E'/A' ratio, early diastolic Doppler flow to early diastolic myocardial velocity (E/E') ratio was calculated.

Magnetic resonance imaging

All participants underwent cardiac magnetic resonance imaging (MRI) on the locally available whole body MRI scanners. A multi-phase, multi-slice volumetric data set was acquired using a fast 2D cine scan using imaging parameters and analyzed as described previously[4].

Statistical analysis

Differences in endpoints between exercise- and control-groups were analyzed by two-way (repeated measures) analysis of variance (ANOVA) using complete cases only. The treatment*time interaction was estimated to assess the effect of the exercise training program on each endpoint. Within-subject comparisons were performed by paired Student's t-tests or Wilcoxon rank test as appropriate, regardless the significance of this interaction. Consequently, the Type I error rate for detecting significant changes from zero may be inflated, which we considered acceptable for this pilot study. We considered a *p*-value of less than 0.05 (2-sided test) as statistically significant. All statistical analyses were performed using SPSS.

Sample size calculation

This pilot study was designed to detect relatively large standardized effect sizes (mean difference divided by the standard deviation) of 1.0 for the various echocardiographic endpoints with 90% power ($\beta = 0.10$), using 2-sided tests with $\alpha = 0.05$. We elected for a 2:1 randomization, with the larger number of patients randomized to the exercise training program. Then, a total of 48 (32 : 16) patients would be required. We finally obtained analyzable information on 47 randomized patients (27 : 20). Consequently, in retrospect, the power of our study was 93%, 75% and 40% to detect effect sizes of 1.0, 0.75 and 0.5, respectively.

RESULTS

Patient characteristics

We invited 230 patients to participate in this study. Forty-eight patients participated (Figure 1, flow chart). The time-consuming nature of the study was the main reason not to participate.

No significant differences were noted between participants and those non-participants with regard to age at the study and age at operation. One patient in the exercise-group dropped out (Figure 1, flow chart). Not all tests were successfully completed both before and after the 3 month (exercise training or control) period. The number of patients included in the analysis per test is given below the caption "Analysis" (Figure 1, flow chart). The characteristics of the 47 participants did not differ statistically significantly between the exercise- and control-groups (Table 1).

ECGs were obtained before and after the training period. Regional ischemia was not seen on the ECG's.

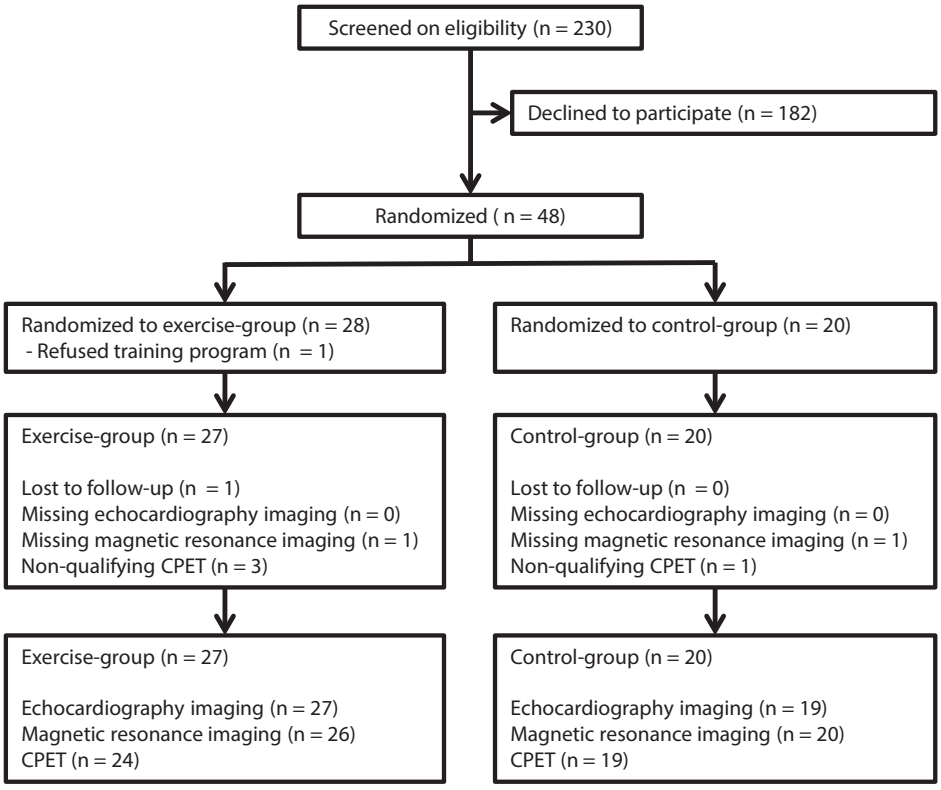

Figure 1: Enrollment
CPET: cardiopulmonary exercise test

Table 1: Baseline patient characteristics

Characteristic	Intervention (n = 27)	Control (n = 20)
Male (n,%)	21 (78%)	14 (70%)
Age at study (years)	15.8 (± 2.7)	16.5 (± 2.6)
10 - <12 years (n,%)	3 (11%)	1 (5%)
12 - <15 years (n,%)	8 (30%)	5 (25%)
15 - <18 years (n,%)	9 (33%)	8 (40%)
18 - 25 years (n,%)	7 (26%)	6 (30%)
Height (cm)	167 (± 11)	170 (± 10)
Weight (kg)	57 (± 14)	61 (± 12)
Oxygen saturation (%)	98 (± 2)	99 (± 1)
Age at ToF operation (months)	10 (± 9)	9 (± 7)
Follow-up since ToF operation (years)	15 (± 2)	16 (± 3)

Number (percentage) or mean (± standard deviation).

In accordance with the inclusion criteria all patients had a ventricular outflow gradient less than 60 mmHg. The maximal outflow gradient measured in the participating patients was 37 mmHg. A gradient greater than 30 was measured in 3 patients, 2 in the training group and 1 in the control group.

Training adherence

Twenty-seven participants in the exercise-group completed the study protocol. Adherence to the training sessions was 89% (median, interquartile range [IQR] 79 – 100). To assess adherence to training intensity, in addition to the monitoring by the local physiotherapist, a random sample of recorded heart rates during exercise training (22% of the exercise-group) was reviewed. All reviewed samples were within the set limits.

Cardio-respiratory fitness

Peak workload at baseline was 170 ± 53 Watt in the exercise-group and 170 ± 38 Watt in the control-group. Peak workload increased significantly during follow-up in the ToF exercise-group compared with the control-group (delta exercise-group 8.4 ± 11.4 Watts; delta control-group −0.1 ± 15.9 Watts; $p = 0.048$). PeakVO_2 at baseline was 35 ± 6 ml/kg/min in the exercise-group and 33 ± 8 ml/kg/min in the control group. There was no significant difference between the change of peakVO_2 in the exercise-group and that in the control-group ($p = 0.14$). In the ToF exercise-group, peakVO_2 significantly increased (delta 2.9 ± 4.0 ml/kg/min; within-subject analysis $p = 0.002$), whereas in the control-group, peakVO_2 did not significantly increase (delta 0.7 ± 5.1 ml/kg/min; within-subject analysis $p = 0.54$).

Echocardiography

The conventional echocardiography parameters at baseline are shown in Table 2. At baseline the parameters did not differ between the exercise- and the control-groups except for MV peak A and MAPSE.

Table 2: Conventional echocardiographic parameters at baseline

	Exercise-group (n = 27)	Control-group (n = 20)	P-value
IVC diameter max/min ratio (mm)	3.73 ± 2.15	5.04 ± 2.72	0.08
Liver vein peak S/D ratio	0.55 ± 0.34	0.59 ± 0.27	0.72
IVSd (mm)	8 ± 2	9 ± 2	0.09
LVPWd (mm)	9 ± 2	9 ± 2	0.45
MAPSE (mm)	17 ± 3	14 ± 2	0.003
TAPSE (mm)	17 ± 4	16 ± 4	0.69
MV Doppler E (cm/s)	99 ± 22	102 ± 20	0.65
MV Doppler A (cm/s)	47 ± 10	58 ± 16	0.006
MV Doppler E/A ratio	2.30 ± 1.27	1.85 ± 0.53	0.16
TV Doppler E (cm/s)	73 ± 15	69 ± 10	0.21
TV Doppler A (cm/s)	44 ± 14	47 ± 11	0.57
TV Doppler E/A ratio	178 ± 61	155 ± 48	0.19
RV outflow gradient (mmHg)	12.3 ± 8.2	12.6 ± 6.7	0.92
LV outflow gradient (mmHg)	3.6 ± 1.5	4.4 ± 1.6	0.13
SVC peak S (cm/s)	43 ± 13	43 ± 18	0.96
SVC peak D (cm/s)	54 ± 14	48 ± 11	0.15

IVC: inferior vena cava; S: systole; D: diastole; IVSd: interventricular septum dimension in diastole; LVPWd: left ventricular posterior wall dimension in diastole; MAPSE: maximal mitral annular plane systolic excursion; TAPSE: maximal tricuspid annular plane systolic excursion; E: early diastole; A: late diastole; SVC: superior vena cava.

TDI echocardiography parameters

TDI parameters in the ToF patients before and after the exercise period are shown in Table 3.

There was no significant difference between the changes in global and regional myocardial function of the exercise-group compared to the control-group. None of the parameters changed after the intervention period, neither in the exercise-group nor in the control-group.

Magnetic resonance imaging

The parameters measured with MRI are shown in table 4. Global size and function did not change after the exercise training in the exercise group compared to the control group.

Table 3: Complete-Case tissue Doppler imaging parameters before and after exercise training

	Exercise-group (n = 27)			Control-group (n = 20)			P-value
	Before	After	Change	Before	After	Change	
Mitral valve							
Isovolumic acceleration (m/s^2)	2.23 ± 1.19	2.01 ± 0.93	−0.22 ± 1.1	2.29 ± 0.78	2.09 ± 0.59	−0.20 ± 0.73	0.95
Peak S' (cm/s)	9.3 ± 2.5	9.1 ± 2.9	−0.2 ± 2.3	9.3 ± 2.1	9.1 ± 2.0	−0.2 ± 1.7	0.99
Time to peak S' (mm)	175 ± 52	184 ± 57	9 ± 52	165 ± 50	164 ± 49	−1 ± 48	0.52
Peak E' (cm/s)	17.9 ± 3.2	17.5 ± 3.5	−0.4 ± 3.4	17.8 ± 3.7	17.5 ± 4.8	−0.3 ± 5.1	0.91
Peak A' (cm/s)	5.7 ± 1.9	5.2 ± 1.8	−0.4 ± 2	6.0 ± 1.9	5.6 ± 1.7	−0.4 ± 1.9	0.97
E'/A' ratio	3.50 ± 1.35	3.65 ± 1.21	0.15 ± 1.21	3.17 ± 0.99	3.31 ± 1.16	0.15 ± 1.31	0.99
E/E' ratio	5.75 ± 1.85	5.90 ± 2.21	0.14 ± 1.44	5.89 ± 1.54	5.42 ± 1.69	−0.47 ± 1.45	0.17
Interventricular septum							
Isovolumic acceleration (m/s^2)	1.96 ± 0.98	2.16 ± 1.10	0.20 ± 1.14	2.20 ± 1.39	2.18 ± 1.06	−0.02 ± 1.36	0.58
Peak S' (cm/s)	7.5 ± 1.5	7.2 ± 1.6	−0.3 ± 1.4	8 ± 1.6	8.5 ± 2.3	0.5 ± 2.1	0.14
Time to peak S' (mm)	152 ± 36	154 ± 37	1 ± 36	145 ± 21	149 ± 20	4 ± 19	0.78
Peak E' (cm/s)	11.9 ± 3.1	11.9 ± 2.6	0 ± 2.3	12.7 ± 2.9	12.8 ± 3.2	0.1 ± 2.8	0.86
Peak A' (cm/s)	5.7 ± 1.7	5.4 ± 1.4	−0.3 ± 1.8	6 ± 1.6	6.2 ± 1.5	0.1 ± 1.8	0.37
Tricuspid valve							
Isovolumic acceleration (m/s^2)	1.86 ± 0.81	2.07 ± 1.12	0.21 ± 1.32	2.01 ± 0.97	1.98 ± 0.87	−0.03 ± 1.77	0.66
Peak S' (cm/s)	9.2 ± 2.7	9.0 ± 2.8	−0.1 ± 1.7	10.0 ± 2.8	10.8 ± 2.9	0.8 ± 2.4	0.15
Time to peak S' (mm)	191 ± 47	185 ± 39	−6 ± 45	187 ± 39	184 ± 33	−4 ± 27	0.84
Peak E' (cm/s)	10.8 ± 4.6	11.5 ± 4.3	0.8 ± 2.6	11.3 ± 3.7	12.1 ± 34	0.9 ± 4.1	0.90
Peak A' (cm/s)	5.3 ± 2.6	5.7 ± 30	0.4 ± 2.4	5.5 ± 2.1	5.5 ± 2.1	4.6 ± 18.1	0.74
E'/A' ratio	2.29 ± 1.29	2.25 ± 1.02	−0.03 ± 1.39	2.24 ± 0.91	2.07 ± 0.86	−0.18 ± 0.97	0.70
E/E' ratio	8.33 ± 4.22	7.27 ± 3.23	−1.06 ± 3.25	7.10 ± 3.45	6.23 ± 2.90	−0.09± 2.08	0.82

Peak S': peak systolic myocardial velocity; peak E': peak early diastolic myocardial velocity; peak A': peak late diastolic myocardial velocity; E/E' and E'/A': early diastolic Doppler flow to early diastolic myocardial velocity. P-values were calculated using two-way analysis of variance. * indicates a *p*-value <0.05 within subject change.

DISCUSSION

The data of this pilot study suggest that aerobic dynamic exercise training does not result in adverse changes of regional systolic and diastolic ventricular performance in children and young adults after surgical correction of ToF. As such, our preliminary data support the general health guidelines that encourage patients with ConHD to participate in sport activities and may add to the knowledge that exercise training in patients with ConHD is safe[1]. From these data it cannot be concluded that all sport activities are

Table 4: Complete-case MRI results

	Exercise-group (n = 26)			Control-group (n = 19)			*p*-value
	Before	After	Change before-after	Before	After	Change before after	
Left ventricle							
EDV_i (ml/m^2)	82 ± 13	81 ± 14	−1 ± 7	86 ± 7	84 ± 11	−2 ± 6	0.77
SV_i (ml/m^2)	48 ± 7	47 ± 8	−1 ± 6	52 ± 5	52 ± 7	−0 ± 5	0.61
mass (g/ m^2)	49 ± 9	49 ± 10	0.6 ± 6.1	48 ± 8	47 ± 8	−1.1 ± 4.2	0.29
Right ventricle							
EDV_i (ml/m^2)	124 ± 32	122 ± 32	−2 ± 13	133 ± 36	132 ± 36	−1 ± 10	0.59
SV_i (ml/m^2)	61 (50 - 77)	56 (51 - 69)	−3 ± 10	55 (52 - 78)	67 (50 - 78)	12 ± 8	0.15
SV_i effective (ml/m^2)	45 ± 10	41 ± 5	−4 ± 18	45 ± 13	44 ± 10	−1 ± 21	0.63
mass (g/ m^2)	21 ± 5	19 ± 4	−1.3 ± 5.1	19 ± 5	19 ± 6	−0.5 ± 4.2	0.57
Pulmonary artery							
Regurgitation fraction (%)	31 ± 14	32 ± 15	1.3 ± 7.4	32 ± 15	36 ± 23	3.5 ± 12.2	0.59

Volume in (ml/m^2) EDV_i indexed end diastolic volume; SV_i indexed stroke volume; RV SV_i effective = right ventricular end diastolic volume – end systolic volume – pulmonary regurgitant volume. Values are shown as mean ± SD and changes are shown as mean (95% confidence interval). P-value relates to the between subjects comparisons, analyzed by two-way ANOVA. * indicates a *p*-value <0.05 within subject change.

safe for every ConHD patient and considering the limited power of the study the data needs to be interpreted with caution. However, since we studied patients with highly abnormal loading conditions of the heart, the information from this pilot study may encourage clinicians to prescribe an exercise training program for their patients with ConHD[16].

A recent review has shown a significant lack of knowledge of alterations of ventricular performance following an exercise training program in patients with ConHD[8]. A total of 29 exercise training studies have been performed in these patients. Six hundred and twenty-one patients participated in these exercise training studies, which were mostly 12 weeks in duration and consisted of dynamic training three times per week. Interestingly, only 2 studies reported on the global cardiac status before and after the exercise training program[8]. Cordina et al. included 6 adult Fontan patients in a 20-week high-intensity resistance exercise training program. Four of the participants underwent cardiac magnetic resonance imaging (MRI) before and after the intervention. An improvement of global ventricular performance was seen, defined as a significant increase in cardiac output. Sklansky et al. included 11 pediatric ToF patients in an 8-week aerobic dynamic exercise training program[8]. An echocardiographic study was performed before and after the training period. The LV dimensions did not significantly change.

Conventional global echocardiographic parameters rely on geometric assumptions. These assumptions do not necessarily hold in patients with ConHD[17]. TDI is less depen-

dent of chamber geometry and enables assessment of global and regional ventricular performance[17]. Changes in regional systolic and diastolic ventricular performance have been recognized as more sensitive markers of deterioration of function than conventional markers in patients with acquired heart disease as well as ConHD[13].

Changes related to acute bouts of exercise in normal but untrained hearts may include enhanced diastolic filling velocities, as has been shown by an increase of peak diastolic velocities measured with TDI during exercise[18]. The proportion of increase in stroke volume that occurs with acute bouts of exercise depends on the training status: the better trained, the more enhanced the diastolic performance, which ultimately contributes to an increase in stroke volume[18, 19].

Prolonged exercise training in healthy subjects (athletes) also results in changes in regional ventricular performance. This performance is enhanced as an increase in peak E' is seen, as well as an increase in the E'/A' ratio, both measured with echocardiography at rest. In addition, strain analysis has supported the findings of enhanced diastolic filling[20]. Combined with an increase of end-diastolic volume, this contributes to enhanced stroke volume[21]. Although most of the strain research in athletes has been performed in adults, the available data confirm these findings in healthy young athletes[19]. Conventional echocardiographic parameters differ between athletes engaged in endurance versus strength exercise, which has not been studied for regional parameters.

In ToF patients, the long-term effects of sequelae following correction, mainly pulmonary regurgitation, induce increased right ventricular end-diastolic volume as well as left-sided changes[6]. This may cause reduced RV as well as LV diastolic and systolic performance[22]. Although the RV global diastolic performance measured by Doppler blood flow in our ToF patients was within the normal range, TDI measurements in the RV walls confirm that RV regional diastolic dysfunction exists[22, 23].

Van den Berg et al. have shown that reduced global ventricular diastolic function seen in ToF patients at rest is impaired to a larger extent during acute stress[22]. In the present pilot study, the data suggest that prolonged exercise training does not negatively affect regional ventricular diastolic function, nor does it affect systolic performance in ToF patients.

Limitations

The sample size in our study is relatively small. We were unable to include exactly the statistically required number of ToF patients. This means that the current data are underpowered to detect effect sizes smaller than 0.75 standard deviations (see also Statistics section). Caution is required in interpreting the results of the study, which has limited generalizability. However, this is the first randomized exercise training trial in pediatric cardiology and considering the complete lack of information in a potentially important and relevant area, we feel that the data are important to be available in the public do-

main. The data may be regarded as an initial proof of concept. We expect this study to stimulate future research in this field.

This study includes the largest homogenous population of ToF patients compared to all previous exercise training studies in patients with ConHD[8]. We were only able to study one type of exercise training. We therefore did not investigate the effect of strength training or high intensity training, both of which have been advocated as alternatives for dynamic aerobic training in acquired heart disease[24, 25].

We measured the echocardiographic parameters at rest. Ideally we would have presented echocardiographic parameters before and after the intervention measured during exercise. However this was not feasible. We believe that effects of exercise training can manifest as changes in cardiac parameters measured at rest, as has been demonstrated for other parameters in healthy subjects[19, 26].

We excluded ToF patients with an outflow gradient of 60 mmHg higher. The actual measured average gradient was low; we therefore could not explore the relation of the outflow gradient with exercise capacity.

There is evidence that acute stress may result in regional ventricular changes, not related to oxygen consumption[5]. We did not find evidence that this translates to changes in response to exercise training. This discrepancy clearly deserves further study. The strengths of this pilot study include the fact that it was carried out prospectively, the patients were randomized, and the training program was well supervised. In this setting it was not feasible to collect information on the longer-term effects of the program.

Clinical relevance

Many patients with ConHD do not exercise and physicians may be reluctant to advise physical activity. In this pilot study we have provided preliminary data suggesting that a training program in ToF patients does not influence regional ventricular performance. This information might help patients and physicians to adhere to current public-health guidelines[16]. This pilot study warrants further investigation.

Conclusion

The preliminary data of our pilot study suggest that regional ventricular performance is well maintained during aerobic dynamic exercise training in patients with corrected ToF. However, more research is needed to confirm the findings.

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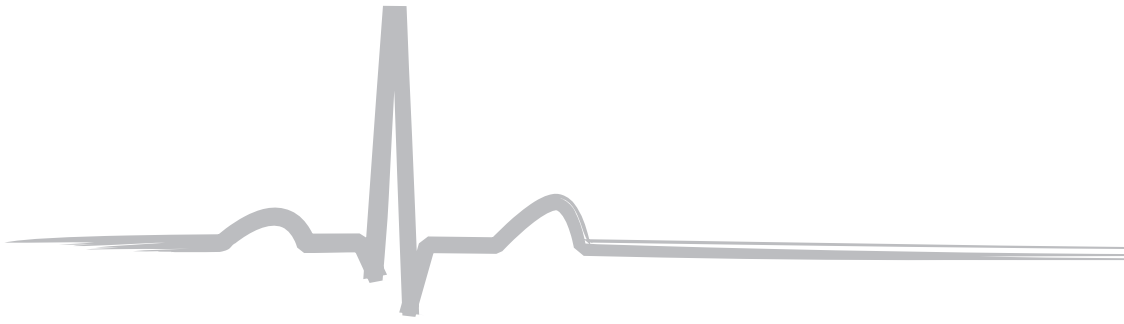
REFERENCES

1. Hirth A, Reybrouck T, Bjarnason-Wehrens B, Lawrenz W, Hoffmann A. Recommendations for participation in competitive and leisure sports in patients with congenital heart disease: A consensus document. *Eur J Cardiovasc Prev Rehabil*. 2006;13:293-299
2. Swift DL, Lavie CJ, Johannsen NM, Arena R, Earnest CP, O'Keefe JH, Milani RV, Blair SN, Church TS. Physical activity, cardiorespiratory fitness, and exercise training in primary and secondary coronary prevention. *Circ J*. 2013;77:281-292
3. Reybrouck T, Mertens L. Physical performance and physical activity in grown-up congenital heart disease. *Eur J Cardiovasc Prev Rehabil*. 2005;12:498-502
4. Robbers-Visser D, Jan Ten Harkel D, Kapusta L, Strengers JL, Dalinghaus M, Meijboom FJ, Pattynama PM, Bogers AJ, Helbing WA. Usefulness of cardiac magnetic resonance imaging combined with low-dose dobutamine stress to detect an abnormal ventricular stress response in children and young adults after fontan operation at young age. *Am J Cardiol*. 2008;101:1657-1662
5. Roche SL, Grosse-Wortmann L, Redington AN, Slorach C, Smith G, Kantor PF, Friedberg MK. Exercise induces biventricular mechanical dyssynchrony in children with repaired tetralogy of fallot. *Heart*. 2010;96:2010-2015
6. van den Berg J, Hop WC, Strengers JL, de Jongste JC, van Osch-Gevers L, Meijboom FJ, Pattynama PM, Bogers AJ, Helbing WA. Clinical condition at mid-to-late follow-up after transatrial-transpulmonary repair of tetralogy of fallot. *J Thorac Cardiovasc Surg*. 2007;133:470-477
7. Norozi K, Wessel A, Alpers V, Arnhold JO, Geyer S, Zoege M, Buchhorn R. Incidence and risk distribution of heart failure in adolescents and adults with congenital heart disease after cardiac surgery. *Am J Cardiol*. 2006;97:1238-1243
8. Duppen N, Takken T, Hopman MT, ten Harkel AD, Dulfer K, Utens EM, Helbing WA. Systematic review of the effects of physical exercise training programmes in children and young adults with congenital heart disease. *Int J Cardiol*. 2013;168:1779-1787
9. van den Berg J, Strengers JL, Wielopolski PA, Hop WC, Meijboom FJ, de Rijke YB, Boomsma F, Bogers AJ, Pattynama PM, Helbing WA. Assessment of biventricular functional reserve and nt-probnp levels in patients with rv volume overload after repair of tetralogy of fallot at young age. *Int J Cardiol*. 2009;133:364-370
10. Borgdorff MA, Bartelds B, Dickinson MG, Steendijk P, de Vroomen M, Berger RM. Distinct loading conditions reveal various patterns of right ventricular adaptation. *Am J Physiol Heart Circ Physiol*. 2013;305:H354-364
11. Lai WW, Geva T, Shirali GS, Frommelt PC, Humes RA, Brook MM, Pignatelli RH, Rychik J, Task Force of the Pediatric Council of the American Society of E, Pediatric Council of the American Society of E. Guidelines and standards for performance of a pediatric echocardiogram: A report from the task force of the pediatric council of the american society of echocardiography. *J Am Soc Echocardiogr*. 2006;19:1413-1430
12. Eidem BW, McMahon CJ, Cohen RR, Wu J, Finkelshteyn I, Kovalchin JP, Ayres NA, Bezold LI, O'Brian Smith E, Pignatelli RH. Impact of cardiac growth on doppler tissue imaging velocities: A study in healthy children. *J Am Soc Echocardiogr*. 2004;17:212-221
13. Friedberg MK, Mertens L. Deformation imaging in selected congenital heart disease: Is it evolving to clinical use? *J Am Soc Echocardiogr*. 2012;25:919-931
14. Schulz KF, Altman DG, Moher D, Group C. Consort 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332

15. Armstrong N, van Mechelen W. Aerobic fitness. *Paediatric exercise science and medicine*. Oxford: Oxford University Press; 2008:97-108.
16. Swan L, Hillis WS. Exercise prescription in adults with congenital heart disease: A long way to go. *Heart*. 2000;83:685-687
17. Klitsie LM, Roest AA, Blom NA, Ten Harkel AD. Ventricular performance after surgery for a congenital heart defect as assessed using advanced echocardiography: From doppler flow to 3d echocardiography and speckle-tracking strain imaging. *Pediatr Cardiol*. 2014;35:3-15
18. Vella CA, Robergs RA. A review of the stroke volume response to upright exercise in healthy subjects. *British journal of sports medicine*. 2005;39:190-195
19. Zdravkovic M, Perunicic J, Krotin M, Ristic M, Vukomanovic V, Soldatovic I, Zdravkovic D. Echocardiographic study of early left ventricular remodeling in highly trained preadolescent footballers. *J Sci Med Sport*. 2010;13:602-606
20. Nottin S, Doucende G, Schuster-Beck I, Dauzat M, Obert P. Alteration in left ventricular normal and shear strains evaluated by 2d-strain echocardiography in the athlete's heart. *The Journal of physiology*. 2008;586:4721-4733
21. Pela G, Bruschi G, Montagna L, Manara M, Manca C. Left and right ventricular adaptation assessed by doppler tissue echocardiography in athletes. *J Am Soc Echocardiogr*. 2004;17:205-211
22. van den Berg J, Wielopolski PA, Meijboom FJ, Witsenburg M, Bogers AJ, Pattynama PM, Helbing WA. Diastolic function in repaired tetralogy of fallot at rest and during stress: Assessment with mr imaging. *Radiology*. 2007;243:212-219
23. Cantinotti M, Lopez L. Nomograms for blood flow and tissue doppler velocities to evaluate diastolic function in children: A critical review. *J Am Soc Echocardiogr*. 2013;26:126-141
24. Kasikcioglu E Fau - Oflaz H, Oflaz H Fau - Akhan H, Akhan H Fau - Kayserilioglu A, Kayserilioglu A. Right ventricular myocardial performance index and exercise capacity in athletes. *Heart Vessels*. 2005; 20:147–152
25. Mandic S, Myers J, Selig SE, Levinger I. Resistance versus aerobic exercise training in chronic heart failure. *Curr Heart Fail Rep*. 2012;9:57-64
26. Rowland T, Unnithan V, Fernhall B, Baynard T, Lange C. Left ventricular response to dynamic exercise in young cyclists. *Med Sci Sports Exerc*. 2002;34:637-642



Chapter 7

The effect of exercise training on wall shear stress and distensibility in the pulmonary artery in children and young adults with Fontan circulation: a randomized controlled trial.

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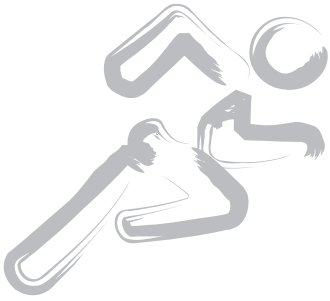


ABSTRACT

Aims: Vascular endothelial-dysfunction is common in the pulmonary artery (PA) in patients with a Fontan circulation. The flow through the Fontan PA depends highly on pulmonary vascular resistance (PVR). A slight increase in PVR can result in decreased ventricular preload and cardiac output, which may contribute to decreased exercise capacity. PVR can be reduced by endothelial released nitric oxide. PA wall shear stress (WSS) regulates this release. We hypothesized that exercise training would enhance WSS and thereby may result in favorable changes in PA endothelial-function.

Methods and results: A multi-center randomized controlled trial was conducted in Fontan patients (10 to 25 years). The exercise-group (n = 28) received a 12-week exercise training program, 3 times per week, the control-group (n = 17) did not. Healthy controls (n = 17) underwent magnetic resonance only at rest whereas Fontan participants at rest and with dobutamine stress (7.5 µg/kg/min). WSS, distensibility and pulsatility of the PA were calculated.

Fontan patients had significantly lower WSS, distensibility and pulsatility compared to healthy controls (WSS: 0.567 ± 0.232 N/m^2 vs 0.819 ± 0.210 N/m^2; $p = 0.001$; distensibility: 0.181 ± 0.054 vs 0.400 ± 0.304; $p = 0.012$; pulsatility: 1.126 ± 0.606 vs 3.400 ± 0.370; $p < 0.001$). The training program did not change WSS, distensibility and pulsatility within the exercise-group, or between the exercise and control-group. At baseline predicted-peakVO_2 was 80% in Fontan patients.

Conclusion: Exercise training did not alter WSS in relatively healthy Fontan patients. Further research is needed to unravel the key to increase WSS and PA endothelial-function.

INTRODUCTION

In patients with univentricular hearts and a Fontan circulation (Fontan patients) the caval veins are directly connected to the pulmonary artery (PA)[1]. As a result of the Fontan operation the pre-pulmonary pump function of the heart is lost[2]. The flow through the PA in this situation depends on the transpulmonary pressure gradient and pulmonary vascular resistance (PVR)[2]. In contrast to healthy peers, a slight increase in PVR results in decrease of ventricular preload and thus cardiac output[2]. This may contribute to decreased exercise capacity in Fontan patients and may relate to poor long-term outcome[1, 3].

Recent studies have explored the possibilities to increase cardiac output in Fontan patients by decreasing PVR with drugs[4, 5]. These studies have, thus far, not been successful, so alternative strategies to influence PVR may be required[4, 5].

Shear stress at the vessel wall and pulsatility in the vessel regulate the release of nitric oxide by the endothelium[6]. Nitric oxide, acting as a local vasodilator, contributes to maintain low PVR[2]. Low wall shear stress (WSS) and loss of distensibility due to loss of pulsatility in the PA have been related to pulmonary vascular dysfunction in the Fontan circulation[7].

In healthy individuals, heart rate and stroke volume increase during exercise. This results in increased NO release and decreased PVR, allowing blood flow through the PA to increase. Prolonged exercise training in healthy subjects results in short term functional adaptation and longer-term structural changes in the large arteries, increasing vascular diameter and decreasing vascular resistance[8]. These mechanisms could be of benefit to influence PA endothelial-function in Fontan patients.

Several studies in small heterogeneous congenital heart disease (ConHD) patient groups, which included Fontan patients, have shown that exercise training can improve exercise capacity[9].

Aim of the study was to assess WSS, distensibility and pulsatility before and after a 12 week standardized aerobic exercise training program in patients with a Fontan circulation. We hypothesized that exercise training would increase WSS, pulsatility and distensibility, thereby improving PA endothelial-function.

METHODS

A multi-center prospective randomized controlled trial was conducted in 5 tertiary referral centers for ConHD in the Netherlands. The study was designed according to Consolidated Standards of Reporting Trials (CONSORT) guidelines[10]. The study is registered at www.trialregister.nl, identification number NTR2731.

Participants

Patients with a Fontan circulation (Fontan patients) between 10 to 25 years were eligible. Seventeen age-matched healthy controls, that did not undergo exercise training, were also included in the study. Exclusion criteria were patients with a ventricular outflow tract obstruction, measured as a pressure drop >60 mmHg and patients that were mentally unable to follow a training program. The study complied with the Declaration of Helsinki. The research protocol was approved by the institutional Ethics Committees. All participants (and/or their parents if required) gave written informed consent.

Intervention

Fontan patients were randomized in a 2 to 1 allocation ratio to either the exercise or control-group by an independent blinded researcher. Stratification was based on gender and age group (10- 12 years, 13-14 years, 15-17 years, and 18-25 years). All participants underwent a standardized stepwise bicycle cardiopulmonary exercise test as described by Bossers et al.[3].

The exercise-group was enrolled in a 12 week, 3 times per week 1 hour standardized aerobic dynamic exercise training program, supervised by local physiotherapists. A heart rate monitor (SR400, Polar Electro BV, Almere, the Netherlands) was given to the patients to ensure execution of the program within the predetermined submaximal heart rate range (60-70% of heart rate reserve). The control-group was instructed to continue their normal daily live. The healthy peers were only included in the baseline measurements.

Magnetic resonance imaging

All participants underwent cardiac magnetic resonance (MR) imaging on the locally available whole body MR scanners (Philips Panorama 1T; Siemens Avanto 1.5T; GE Signa 1.5T; GE Discovery 1.5T; Philips Achieva 1.5T and Philips Ingenia 1.5T) according to previously described methods, at baseline and directly after the 12 week intervention period[11]. Briefly, MR imaging was performed using a phase-contrast (PC) acquisition with a unidirectional velocity encoding range of 60 to 120 cm/s to measure the blood flow inside the PA. In-plane resolution of PC-MR images was between 1.13 and 1.25 mm, slice thickness was 6 mm. This protocol resulted in flow measurements with 18-30 frames per cardiac cycle. Images were acquired and averaged over 3 heart cycles to diminish the effect of respiration. Dobutamine was administered to mimic physical exercise at a rate of 7.5 µg/kg/min. Low-dose dobutamine stress images were only acquired when logistically possible and if the patient consented. Flow measurements were repeated after reaching a steady heart rate, using the same parameters as in the rest conditions. Contours of the pulmonary artery were drawn semi-automatically with the software package QFLOW (Medis Medical Imaging Systems, Leiden, the Netherlands).

Wall shear stress, distensibility and pulsatility

In order to assess local WSS, distensibility and pulsatility, we used an algorithm which adapted from Duivenvoorden et al.[12]. In short, blood velocities were calculated inside the contours of the pulmonary arteries by using PC-MR phase difference images. The cross-section was divided into four segments with 10 degrees of overlap. In each segment, the velocities were projected onto one plane. In this plane, only velocities located within an inward distance of 0.5 pixels and 3 pixels were excluded. A second order curve fit was applied on the projected velocities, while forcing blood velocity to be zero at the lumen wall, to calculate the local spatial derivative of the velocity perpendicular to the wall, wall shear rate. WSS was calculated by multiplying WSR with the blood viscosity which was set to $3.2\ 10^{-3}$ Pa·s for all time intervals. The WSS values of 4 segments were averaged to obtain mean cross-sectional WSS which was necessary to eliminate the adverse effect of complex flow on the WSS estimation.. For the analysis, cardiac cycle averaged WSS was calculated.

Distensibility was defined as the maximum change in the cross-sectional area within one cardiac cycle and calculated as in the following formula:

(maximal area (mm^2) – minimal area (mm^2))/maximal area (mm^2)

Pulsatility was defined as the flow change within one cardiac cycle and calculated as in the following formula:

(maximal flow rate (ml/sec) - minimal flow rate (ml/sec))/mean flow rate (ml/sec)

WSS, distensibility and pulsatility were calculated at one cross-section in the left pulmonary artery (LPA) in Fontan patients. In healthy controls WSS, distensibility and pulsatility were calculated in the right pulmonary artery (RPA). LPA was measured in Fontan patients due to due to the short distance between the connection of the superior vena cava and the first branching point in the RPA. LPA and RPA do not differ in absolute blood flow and peak velocity, as shown by Robbers et al.[7].

Statistical analysis

Differences in parameters between Fontan patients and healthy controls were analyzed by independent t-tests. Differences in parameters between Fontan exercise-group and Fontan control-group were analyzed by two-way (repeated measures) ANOVA. Within group (Fontan exercise-group and Fontan control-group) differences from baseline to follow-up were analyzed by paired Student's t-tests. We considered a *p*-value of 0.05 (2-sided test) as statistically significant.

RESULTS

Baseline characteristics

Forty-five patients participated in this study (figure 1). Age at study and age at Fontan completion did not significantly differ between the participants and the non-participants (n = 87). Significantly more female than male patients declined to participate.

We specified 3 groups, a Fontan exercise-group (n = 28), a Fontan control-group (n = 17) and a healthy peer control-group (n = 17).

Two patients in the Fontan exercise-group dropped out. We were able to analyze the MRI images of 20 of the 26 patients in the Fontan exercise group and of 12 of the 17 patients in the Fontan control-group (figure 1).

Gender, age at study, length and weight did not significantly differ between the healthy controls and the Fontan patients (table 1). Baseline characteristics between the Fontan exercise-group and the Fontan control-group did not significantly differ either (table 1).

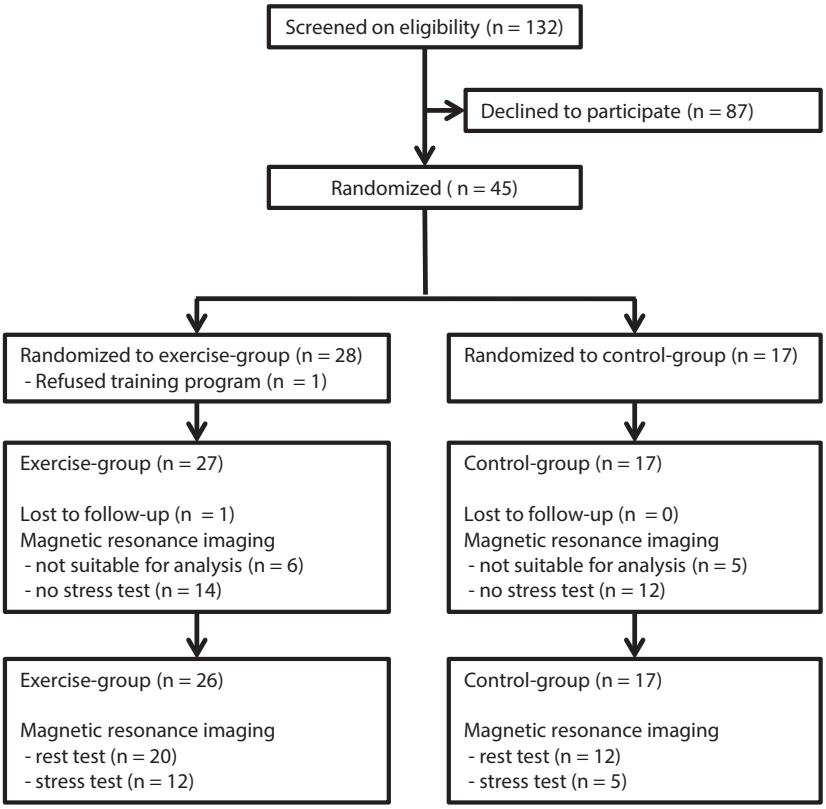


Figure 1: Enrollment

Table 1: Baseline characteristics, healthy controls and Fontan patients

	Healthy controls	All Fontan patients	Randomization (Fontan patients)	
	(n = 17)	(n = 32)	Exercise-group (n = 20)	Control-group (n = 12)
Male (n)	8 (47%)	23 (72%)	14 (70%)	9 (75%)
Length (cm)	164 ± 10	160 ± 14	160 ± 16	160 ± 11
Weight (kg)	52 ± 11	49 ± 14	52 ± 15	46 ± 11
Age (yrs)	13 ± 2	15 ± 4	15 ± 4	15 ± 4
Age at Fontan (yrs)		3.5±1.5	3.6 ± 1.3	3.4 ± 1.8
Follow-up post Fontan (yrs)		11 ± 3	11 ± 3	11 ± 4
Oxygen saturation (%)		95 ± 2	95 ± 2	94 ± 2
Percentage predicted peak VO_2 (%)		82 ± 18	78 ± 18	87 ± 17
Dominant ventricle				
Left		23 (72%)	14 (70%)	9 (75%)
Right		9 (28%)	6 (30%)	3 (25%)
Fontan type				
Intra-atrial lateral tunnel		17 (53%)	11 (55%)	6 (50%)
Extra cardiac conduit		13 (41%)	8 (40%)	5 (42%)
Conversion		2 (6%)	1 (5%)	1 (8%)
Medication				
Oral anticoagulants/platelet inhibitors		32	20	12
Beta-blockers		3	3	0
Digoxine		1	0	1
Arrhythmic event in history		6	4	2
Post Fontan interventions		5	2	3

P-value based on independent t-test (indicated by *); healthy controls vs all patients and Fontan exercise-group vs Fontan control-group.

Adherence to exercise training

Twenty Fontan patients were randomized to the exercise-group. Attendance rate was 92% (median, inter quartile rage 78 - 100%). The heart rate monitors showed that the training intensity was within the set heart rate range during exercise.

In pre- and post-training period exercise tests no difference was observed for peakVO_2 and peak workload.

Differences in wall shear stress, distensibility, pulsatility and flow between healthy controls and Fontan patients

Healthy controls had significantly higher WSS (1.4 times higher), distensibility (2.2 times higher), pulsatility (3 times higher) and flow (1.8 times higher) in the PA as well as a greater maximum area of the PA (1.2 times greater) than Fontan patients (table 2).

Table 2: Healthy controls vs Fontan patients at baseline

	Healthy controls (n = 17)	Fontan patients (n = 32)	*p*-value
Wall shear stress (N/m^2)	0.82 ± 0.21	0.57 ± 0.23	0.001
Distensibility index	0.40 ± 0.30	0.18 ± 0.05	0.012
Mean area (mm^2)	157 ± 46	155 ± 53	0.873
Max area (mm^2)	209 ± 55	171 ± 56	0.031
Pulsatility index	3.40 ± 0.37	1.13 ± 0.61	< 0.001
Mean flow (ml/s)	51 ± 14	29 ± 6	< 0.001
Heart rate (bpm)	73 ± 11	71 ± 14	0.666

P-value based on independent t-test.

Changes in wall shear stress, distensibility pulsatility and flow in Fontan patients at follow-up

WSS, distensibility, pulsatility and flow did not change after the intervention period within the Fontan exercise-group and Fontan control-group. The variation in all parameters as observed from baseline to follow-up in the Fontan exercise-group was not significantly different from the Fontan control-group (table 3).

Table 3: Measurements before and after the exercise training program in Fontan patients

	Fontan exercise-group (n = 20)			Fontan control-group (n = 12)			*p*-value
	Before	After	Change	Before	After	Change	
LPA							
Wall shear stress (N/m^2)	0.55 ± 0.23	0.54 ± 0.23	−0.012 ± 0.152	0.59 ± 0.24	0.62 ± 0.32	0.024 ± 0.158	0.534
Distensibility index	0.18 ± 0.06	0.20 ± 0.0	0.012 ± 0.093	0.179 ± 0.055	0.18 ± 0.07	−0.002 ± 0.052	0.620
Mean area (mm^2)	158 ± 51	155 ± 53	−2 ± 43	150 ± 59	156 ± 69	5 ± 27	0.581
Max area (mm^2)	174 ± 54	174 ± 57	0 ± 45	165 ± 61	171 ± 75	6 ± 30	0.674
Pulsatility index	1.11 ± 0.94	1.26 ± 0.61	0.147 ± 0.668	0.89 ± 0.43	0.82 ± 0.37	0.071 ± 0.284	0.293
Mean flow (ml/s)	29 ± 6	28 ± 6	−2 ± 5	27 ± 6	29 ± 8	2 ± 5	0.078
Heart rate (bpm)	70 ± 15	68 ± 15	−2 ± 11	73 ± 14	72 ± 11	−2 ± 16	0.972

P-value relates to the between subjects comparisons, analyzed by two-way ANOVA; paired t-test within group, $p < 0.05$ is indicated by *.

Measurements of wall shear stress at rest and with dobutamine stress in Fontan patients

In general, WSS measured during dobutamine stress was significantly increased compared to rest (2-way ANOVA, $p < 0.001$). However, at the follow-up assessment of the control group, the WSS increase after dobutamine did not reach statistically significance ($p = 0.084$) (figure 2).

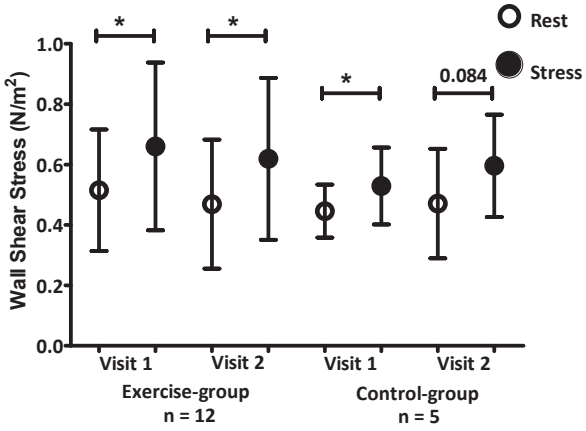


Figure 2: Wall Shear Stress rest and stress
P-value based on paired t-test. * $p < 0.05$.

Distensibility, mean and maximal area in the LPA at dobutamine stress did not significantly change compared to the rest measurement in both the exercise and control-group.

DISCUSSION

This randomized controlled trial demonstrated that a 12 week aerobic exercise training program does not change wall shear stress, distensibility and pulsatility in the pulmonary arteries in Fontan patients. As WSS is an important determinant of NO-release mediated decrease of PVR, this suggests that PVR did not change. These findings add to the understanding of factors contributing to abnormal PA endothelial-function.

Abnormal PA endothelial-function is common after the Fontan procedure and relates to the abnormal flow throughout the different stages towards and after completion of the Fontan circulation (total cavopulmonary connection)[1]. This relates to abnormal quantity of flow before the partial cavopulmonary connection and a highly abnormal, less pulsatile, flow pattern thereafter[13]. These factors have been associated with impaired pulmonary artery function[13].

As a result of the loss of the pre-pulmonary pump, ventricular preload is highly dependent on pulmonary vascular function in these patients[2, 7]. PVR directly relates to PA endothelial-function which is mediated by NO[2, 6, 8]. Endothelial NO is released under the influence of shear stress at the vessel wall and of distensibility and pulsatility in the vessel[2, 6, 8]. In Fontan patients, PA endothelial-function is hampered by a decrease of WSS, distensibility and pulsatility, as confirmed in the present study. This may result in a decrease of NO release[7].

It has been demonstrated that physical exercise training can result in changes in the large arteries of trained healthy subjects. Training results in adaptation of vasodilator capacity as well as in arterial remodeling[6]. During exercise WSS increases. Short term changes of exercise training are characterized by increased vasodilatation potential[8]. The longer-term effect of exercise training includes NO-dependent vascular remodeling, resulting in enlarged arterial diameter[8]. Subsequently, the increase in arterial diameter will result in decrease of WSS, with the effect that further functional adaptation and remodeling does not occur[8].

As in Fontan patients, PA WSS and distensibility are decreased in patients with pulmonary hypertension (PAH)[14]. In PAH patients therapy consists of (pulmonary) vasodilator drugs which reduce PVR and increases cardiac output in this population[14]. Results of trials with vasodilator drugs in Fontan patients have shown equivocal results[5, 15-17].

Studies using the endothelin antagonist bosentan have not shown beneficial results in Fontan patients[5, 15]. In the studies that have administered phosphodiesterase 5 inhibitor sildenafil, an increase in exercise performance and single ventricular stroke volume and a decrease of PVR has been noted[16, 17]. Sildenafil related improvement in exercise capacity was particularly noted in those Fontan patients who had a poor baseline exercise capacity[16]. An intervention study in which sildenafil was administered to a relative young and healthy cohort of Fontan patients for 6 weeks failed to show significant improvement in exercise capacity, but showed improved ventilatory efficiency[4]. The lack of significant peakVO_2 increase was attributed to the relative healthy cohort, reducing the room for improvement of exercise capacity[16]. The difference in effect as shown in studies using bosentan or sildenafil most likely relate to differences in their mode of action. Endothelin expression is enhanced in patients with a failing Fontan circulation[18]. Inhibition of the expression by bosentan will be mostly effective in those patients. Sildenafil inhibits, in all patients, phosphodiesterase-5, which increases cyclic GMP, part of the NO pathway, leading to pulmonary vasodilatation[17]. This would endorse the theory that NO release is altered in Fontan patients, as a result of vascular dysfunction[7, 16].

In contrast to drug intervention studies, well-designed exercise training programs in Fontan patients have shown improved exercise capacity. In 1 study it was shown that cardiac output increased following exercise training[9, 19]. In analogy to the sildenafil studies, Fontan patients with a poorer baseline exercise capacity were more likely to enhance their exercise capacity than those with higher baseline values, which was confirmed in our of Fontan patients with relatively well preserved baseline clinical state[3, 16]. This is in contrast to the clear improvement in exercise performance in patients operated for tetralogy of Fallot of similar age who underwent the same exercise training protocol[20]. In acquired heart disease in adults, characteristics of arterial function have not shown a direct relationship with maximal exercise parameters. Furthermore, the effects of exercise

training on arterial function have differed importantly throughout studies, which may in part depend on the underlying type of disease[21, 22].

A potential problem in the use of sildenafil is side-effects that occur in relatively high percentage of patients. These mainly include headache and flushing. In contrast, the majority of the exercise training program studies did not encounter any exercise related side-effects[4, 9]. Exercise training lacks drug related side-effects, contributes to the reduction of obesity commonly seen in ConHD patients, may increase physical activity levels, as recommended in current health guidelines, and contributes to an increase of domains of health related quality of life[23-25].

The exercise training program described in our study did not change measured parameters related to PA endothelial-function. This could indicate that the exercise training program did not influence the release of NO and PVR. It should be noted that our participants had a relative high peakVO_2 at baseline[26].

There may be several reasons why we did not find any changes following an extensive training program with good adherence. The duration of the training program may have been too short. The type of training may not have been adequate or the hypothesis that exercise training may improve PA endothelial-function in these patients may be invalid.

WSS calculations were based on the actual velocity measured in vivo with PC-MRI. Shear stress measurements are subject to variations because of interobserver variability in lumen segmentation. In order to prevent interobserver variability, the segmentations were performed in one go and by one person (ND). To calculate WSS, we assumed a parabolic curve of flow velocities across the vessel diameter[12]. This is a simplification of reality, as the flow profile will most likely not be parabolic due to the branched pattern of the PA system[27]. Computational fluid dynamics (CFD) simulations are the golden standard to assess flow velocity profiles and WSS. A recent study showed that PC-MRI is as accurate as CFD in assessing WSS patterns[28]. Due to lack of pulsatility, and the anatomy of the Fontan circuit, blood flow inside Fontan circuit has a complex pattern which may cause some errors in 2DPC-MRI measurement such as intra-voxel dephasing. By taking the mean WSS per cross-section, we calculated a general WSS value less sensitive to the local measurement errors

In this study distensibility was assessed as the relative change in PA area. Since relative changes in the PA dimensions over the cardiac cycle result from both the arterial stiffness and the pressure variations, the observed lack in changes in distensibility after a period of a standardized training protocol might be caused by counteracting influences of arterial stiffness and pulse pressure. Since pulsatility in flow did not change due to a training protocol, these data make it plausible that the arterial stiffness did not change over the study period.

Results were obtained using simulated exercise with dobutamine. There are differences between the circulatory response between physiological and pharmacological

stress, however dobutamine mimics physical stress at low dose.[29]. As described by Robbers et al. dobutamine in low dose increases heart rate and cardiac index in young Fontan patients[30]. Results (data not shown) in the current study were similar with respect to the effect type and size.

Pre-study sample size calculations were hampered by a lack of data on the effect of exercise training on non-invasive parameters of PA endothelial-function in Fontan patients. However, patients served as their own controls, which generally increases the power of a study.

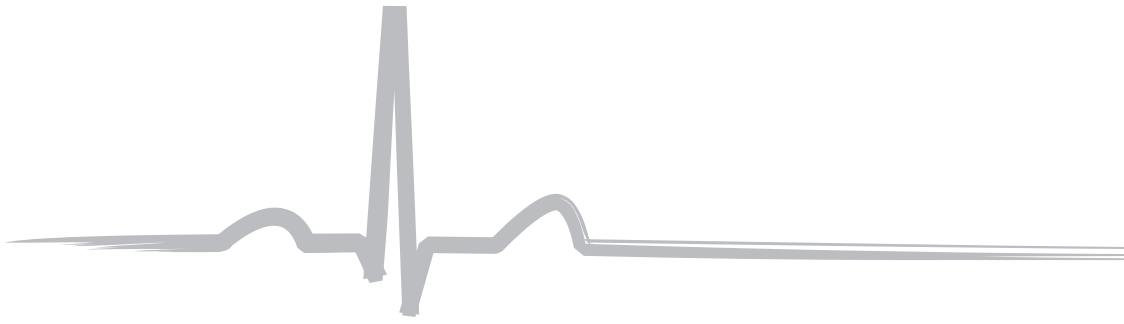
In conclusion, WSS, distensibility and pulsatility, which are lower in Fontan patients than in healthy peers, did not change in response to exercise training in a relatively healthy group of Fontan patients. Considering the important clinical need to influence PA endothelial-function in these patients, further research is needed to assess the potential of exercise training to enhance PA endothelial-function in Fontan patients.

REFERENCES

1. Gewillig M. The fontan circulation. *Heart*. 2005;91:839-846
2. Gewillig M, Brown SC, Eyskens B, Heying R, Ganame J, Budts W, La Gerche A, Gorenflo M. The fontan circulation: Who controls cardiac output? *Interact Cardiovasc Thorac Surg*. 2010;10:428-433
3. Bossers SS, Helbing WA, Duppen N, Kuipers IM, Schokking M, Hazekamp MG, Bogers AJ, Ten Harkel AD, Takken T. Exercise capacity in children after total cavopulmonary connection: Lateral tunnel versus extracardiac conduit technique. *J Thorac Cardiovasc Surg*. 2014;1:1-8
4. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, Hanna BD, Wernovsky G, Paridon SM, Rychik J. Impact of oral sildenafil on exercise performance in children and young adults after the fontan operation: A randomized, double-blind, placebo-controlled, crossover trial. *Circulation*. 2011;123:1185-1193
5. Schuuring MJ, Vis JC, van Dijk AP, van Melle JP, Vliegen HW, Pieper PG, Sieswerda GT, de Bruin-Bon RH, Mulder BJ, Bouma BJ. Impact of bosentan on exercise capacity in adults after the fontan procedure: A randomized controlled trial. *Eur J Heart Fail*. 2013;15:690-698
6. Green DJ, Spence A, Rowley N, Thijssen DH, Naylor LH. Vascular adaptation in athletes: Is there an 'athlete's artery'? *Experimental physiology*. 2012;97:295-304
7. Robbers-Visser D, Helderman F, Strengers JL, van Osch-Gevers L, Kapusta L, Pattynama PM, Bogers AJ, Krams R, Helbing WA. Pulmonary artery size and function after fontan operation at a young age. *J Magn Reson Imaging*. 2008;28:1101-1107
8. Green DJ. Exercise training as vascular medicine: Direct impacts on the vasculature in humans. *Exerc Sport Sci Rev*. 2009;37:196-202
9. Duppen N, Takken T, Hopman MT, ten Harkel AD, Dulfer K, Utens EM, Helbing WA. Systematic review of the effects of physical exercise training programmes in children and young adults with congenital heart disease. *Int J Cardiol*. 2013;168:1779-1787
10. Schulz KF, Altman DG, Moher D, Group C. Consort 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332
11. Robbers-Visser D, Luijnenburg SE, van den Berg J, Roos-Hesselink JW, Strengers JL, Kapusta L, Moelker A, Helbing WA. Safety and observer variability of cardiac magnetic resonance imaging combined with low-dose dobutamine stress-testing in patients with complex congenital heart disease. *Int J Cardiol*. 2011;147:214-218
12. Duivenvoorden R, Vanbavel E, de Groot E, Stroes ES, Disselhorst JA, Hutten BA, Lameris JS, Kastelein JJ, Nederveen AJ. Endothelial shear stress: A critical determinant of arterial remodeling and arterial stiffness in humans--a carotid 3.0-t mri study. *Circ Cardiovasc Imaging*. 2010;3:578-585
13. Gewillig M, Brown SC, Heying R, Eyskens B, Ganame J, Boshoff DE, Budts W, Gorenflo M. Volume load paradox while preparing for the fontan: Not too much for the ventricle, not too little for the lungs. *Interact Cardiovasc Thorac Surg*. 2010;10:262-265
14. Tang BT, Pickard SS, Chan FP, Tsao PS, Taylor CA, Feinstein JA. Wall shear stress is decreased in the pulmonary arteries of patients with pulmonary arterial hypertension: An image-based, computational fluid dynamics study. *Pulmonary circulation*. 2012;2:470-476
15. Ovaert C, Thijs D, Dewolf D, Ottenkamp J, Dessy H, Moons P, Gewillig M, Mertens L. The effect of bosentan in patients with a failing fontan circulation. *Cardiol Young*. 2009;19:331-339
16. Hager A, Weber R, Muller J, Hess J. Predictors of sildenafil effects on exercise capacity in adolescents and adults with fontan circulation. *Clin Res Cardiol*. 2014;3:1-6

17. Van De Bruaene A, La Gerche A, Claessen G, De Meester P, Devroe S, Gillijns H, Bogaert J, Claus P, Heidbuchel H, Gewillig M, Budts W. Sildenafil improves exercise hemodynamics in fontan patients. *Circ Cardiovasc Imaging*. 2014;7:265-273
18. Ishida H, Kogaki S, Ichimori H, Narita J, Nawa N, Ueno T, Takahashi K, Kayatani F, Kishimoto H, Nakayama M, Sawa Y, Beghetti M, Ozono K. Overexpression of endothelin-1 and endothelin receptors in the pulmonary arteries of failed fontan patients. *Int J Cardiol*. 2012;159:34-39
19. Cordina RL, O'Meagher S, Karmali A, Rae CL, Liess C, Kemp GJ, Puranik R, Singh N, Celermajer DS. Resistance training improves cardiac output, exercise capacity and tolerance to positive airway pressure in fontan physiology. *Int J Cardiol*. 2013;168:780-788
20. Duppen N, Kapusta L, de Rijke YB, Snoeren M, Kuipers IM, Koopman LP, Blank AC, Blom NA, Dulfer K, Utens EMWJ, Hopman MTE, Helbing WA. The effect of exercise training on cardiac remodelling in children and young adults with corrected tetralogy of fallot or fontan circulation: A randomized controlled trial. *Int J Cardiol*. 2015;179:97-104
21. Vinet A, Karpoff L, Walther G, Startun A, Obert P, Goret L, Dauzat M, Perez-Martin A. Vascular reactivity at rest and during exercise in middle-aged obese men: Effects of short-term, low-intensity, exercise training. *Int J Obes (Lond)*. 2011;35:820-828
22. Fujimoto N, Prasad A, Hastings JL, Bhella PS, Shibata S, Palmer D, Levine BD. Cardiovascular effects of 1 year of progressive endurance exercise training in patients with heart failure with preserved ejection fraction. *Am Heart J*. 2012;164:869-877
23. Pemberton VL, McCrindle BW, Barkin S, Daniels SR, Barlow SE, Binns HJ, Cohen MS, Economos C, Faith MS, Gidding SS, Goldberg CS, Kavey RE, Longmuir P, Rocchini AP, Van Horn L, Kaltman JR. Report of the national heart, lung, and blood institute's working group on obesity and other cardiovascular risk factors in congenital heart disease. *Circulation*. 2010;121:1153-1159
24. Dulfer K, Duppen N, Kuipers IM, Schokking M, van Domburg RT, Verhulst FC, Helbing WA, Utens EM. Aerobic exercise influences quality of life of children and youngsters with congenital heart disease: A randomized controlled trial. *The Journal of adolescent health: official publication of the Society for Adolescent Medicine*. 2014;2:1-8
25. Takken T, Giardini A, Reybrouck T, Gewillig M, Hovels-Gurich HH, Longmuir PE, McCrindle BW, Paridon SM, Hager A. Recommendations for physical activity, recreation sport, and exercise training in paediatric patients with congenital heart disease: A report from the exercise, basic & translational research section of the european association of cardiovascular prevention and rehabilitation, the european congenital heart and lung exercise group, and the association for european paediatric cardiology. *Eur J Prev Cardiol*. 2012;19:1034-1065
26. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: Comparative severity, correlates, and prognostic implication. *Circulation*. 2005;112:828-835
27. Reneman RS, Arts T, Hoeks AP. Wall shear stress--an important determinant of endothelial cell function and structure--in the arterial system in vivo. Discrepancies with theory. *Journal of vascular research*. 2006;43:251-269
28. Cibis M, Potters WV, Gijsen FJ, Marquering H, vanBavel E, van der Steen AF, Nederveen AJ, Wentzel JJ. Wall shear stress calculations based on 3d cine phase contrast mri and computational fluid dynamics: A comparison study in healthy carotid arteries. *NMR in biomedicine*. 2014;27:826-834
29. Helbing WA, Luijnenburg SE, Moelker A, Robbers-Visser D. Cardiac stress testing after surgery for congenital heart disease. *Curr Opin Pediatr*. 2010;22:579-586

30. Robbers-Visser D, Jan Ten Harkel D, Kapusta L, Strengers JL, Dalinghaus M, Meijboom FJ, Pattynama PM, Bogers AJ, Helbing WA. Usefulness of cardiac magnetic resonance imaging combined with low-dose dobutamine stress to detect an abnormal ventricular stress response in children and young adults after fontan operation at young age. *Am J Cardiol*. 2008;101:1657-1662



Chapter 8

Aerobic exercise influences quality of life of children and youngsters with congenital heart disease: a randomized controlled trial.

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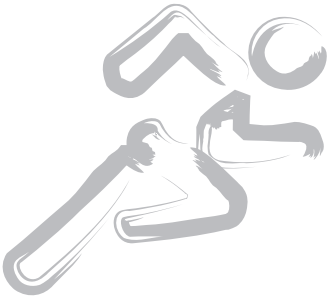


ABSTRACT

Purpose: To evaluate effects of an exercise program on health related quality of life (HRQoL) in children and adolescents with Tetralogy of Fallot (ToF) or a Fontan circulation.
Methods and results: Stratified, randomized, controlled intervention study conducted in 5 participating centers of pediatric cardiology in the Netherlands.
In total, 93 patients, aged 10 – 25, with surgical repair for tetralogy of Fallot or with a Fontan circulation for single-ventricle physiology were included. They were randomly allocated with a ratio of 2:1 to: a) a 12-week period with an exercise program for 3 times per week or b) to a control group. Randomization was stratified by age, gender, and cardiac diagnosis. At baseline and follow-up after 12 weeks, all participants completed web-based age-appropriate HRQoL questionnaires. Primary analyses involved change in HRQoL during follow-up. Secondary analyses concerned influence of cardiac diagnosis and comparison with normative data.

Respectively 48 (86%) and 32 (86%) patients in the exercise group and control group completed all questionnaires at baseline and follow-up. Compared with the control group, children, aged 10 – 15, in the exercise group improved significantly on self-reported cognitive functioning, $p < .05$, $r = .30$, and parent-reported social functioning, $p < .05$, $r = 0.30$. Youngsters aged 16 to 25 did not change their HRQoL. Cardiac diagnosis had no influence on pre-post changes.

Children and youngster in this study reported comparable or better HRQoL than norm groups.
Conclusions: Participation in an exercise program improved HRQoL of children with ToF or a Fontan circulation, especially in those with low baseline HRQoL.

INTRODUCTION

Nowadays, at least 85% of children born with congenital heart disease (ConHD) survive into adulthood[1]. These children may experience long-term physical morbidity. Compared to healthy peers, adolescents with severe ConHD have reduced exercise capacity[2, 3].

Although children and adolescents with ConHD are recommended to participate in physical activity, as stated in the guidelines from the European Society of Cardiology[4], they do not perform the same amount of dynamic physical activity compared with healthy peers[5]. Reduced exercise capacity has been associated with reduced health related quality of life (HRQoL) in children with ConHD[6]. Adolescents with mild or severe ConHD and reduced exercise capacity, reported lower overall HRQoL than their healthy peers. Those with severe ConHD, i.e. Fontan circulation, reported a worse HRQoL than those with mild ConHD[7].

The few studies conducted into an exercise program showed promising results regarding improving exercise capacity and physical activity in adolescents with ConHD[8, 9]. The studies, with small samples, showed that peak oxygen consumption improved, as did workload[10], exercise time[10], and daily physical activity[11]. However, little is known about the impact of an exercise program on HRQoL in these adolescents.

In adults with ConHD, HRQoL improved after an exercise program[12]. Until now, three studies, using small samples, have examined the effect of a 3-day sports camp[13, 14], or a 12-week exercise program[15] on self-perceived health status in adolescents with ConHD. To our knowledge, no *randomized controlled trial* in adolescents with ConHD has been done to examine the effect of an exercise program on HRQoL.

The present prospective, multicenter study is a randomized controlled trial into the effect of a standardized exercise program on HRQoL in a relatively large cohort of patients, aged 10 to 25, with either surgical repair for ToF or a Fontan circulation. Two-third of the ToF and Fontan patients included were randomized to an aerobic exercise program; the remaining one-third served as controls. We hypothesized that an exercise program would improve HRQoL in these patients.

The present study's aim was to answer the research questions:

- What is the effect of a 12-week exercise program versus a control group in patients aged 10-25 with ToF or Fontan circulation, on their health related quality of life?
- What is the influence of cardiac diagnosis on the HRQoL-effects of the exercise program?
- What is the level of health related quality of life, at baseline and post assessment, in patients who participated in the exercise program and in the control group, compared to that of same aged peers from the general population?

METHODS

This randomized controlled trial is designed according to the CONSORT guidelines[16].

Inclusion/exclusion

Included were patients, aged 12 to 20, who underwent cardiac surgery before the age of 2 years for ToF, and patients, aged 10 to 25, who underwent surgery for single-ventricle physiology (intra-cardiac or extra-cardiac tunnel type of Fontan-completion, at least 2 stages) before the age of 6 years. Patients were treated at one of the 5 participating centers of pediatric cardiology in the Netherlands: Academic Medical Center Amsterdam, Erasmus Medical Center Rotterdam, Leiden University Medical Center, University Medical Center Radboud, and University Medical Center Utrecht.

Excluded were patients with: contra-indications for exercise, mental retardation, standard contra-indications for magnetic resonance imaging (MRI), or a ventricular outflow obstruction (peak Doppler gradient > 60 mm Hg).

Randomization

After informed consent had been obtained, patients received an anonymous study code and were invited for medical and psychological *baseline* assessments. Thereafter, a 'blind' independent researcher allocated the patients to the exercise program or the control group (ratio 2:1) according to restricted randomization. We formed balanced groups through stratification by age group, gender, and ConHD, together with fixed block sizes of 3. In addition, the overall study sample size (93) is a multiple of the block size (3), which guaranteed that the number of participants assigned to each treatment group would be equal. Within each fixed block, the first and second patients in the stratification-group (e.g. age-group 10-12, boys, Fontan) were randomized through envelopes. The randomization of the third patient within the randomization block depended on the previous two randomizations.

Intervention

The standardized exercise program consisted of 3 training sessions of 1 hour per week, during a 3-month period. Patients who already participated in sports activities were instructed to continue these activities and participate in the exercise program 2 times a week. The exercise program consisted of 10 minutes warming-up, 40 minutes aerobic dynamic cardiovascular training, and 10 minutes cooling down. Cardiovascular training included brisk walking/jogging/running/bicycle exercises, and dynamic play. Participants were given a heart rate monitor and were instructed to perform their exercises within the given heart range (resting heart rate plus 60-70 % of the heart rate reserve, for details see Duppen et al. 2013[8] and Tikkanen et al. 2012[9]). This range was determined

by the ergometer-test performed at the baseline assessment. They were not allowed to train above the prescribed range.

Since training intensity level was monitored and adjusted according to a pre-determined heart rate range, workload was directly adjusted to heart rate levels. This meant that improvements were directly reflected in individualized workloads. The intensity range was programmed in their heart rate monitor; an alarm informed them when they did not adhere to this range.

The program was performed group-wise, under supervision of a trained and licensed physiotherapist in local centers throughout the Netherlands. The same researcher (ND) visited all participating physiotherapists prior to the start of the program and visited them thereafter when needed, to ensure standardized implementation of the exercise program. The control group continued their normal daily live and was invited for a baseline and a follow-up medical and psychological assessment.

Assessment procedure

The ethics-committee review boards of all 5 medical centers approved the research protocol. All eligible patients and their parents were approached uniformly through a patient-information letter and completed the same psychological instruments at 2 points in time. The baseline psychological assessment, a *web-based* questionnaire and a semi-structured interview by phone, took place no longer than 2 months before the start of the exercise program, and 1-3 days before the baseline cardiac assessment in the hospital. The second psychological assessment was performed no later than one month after completion of the exercise program, and no more than 2 weeks after the second cardiac assessment in the medical center. Assessments for control groups were performed at comparable time points.

Semi-structured interview

A semi-structured interview[17] was completed by phone. Separate questions were included for children, aged 10 – 15, adolescents/young adults, aged 16 – 25, and for parents of children/adolescents, aged 10 – 18. In these interviews biographical data, such as household composition, educational level, social participation, professional mental health care consumption, and perceived body image were assessed.

Socioeconomic status of parents was divided into low, middle, and high occupational level[18].

Web-based questionnaire

The web-based questionnaire consisted of a child-version and a parent-version. It encompassed the following internationally well-known, age-appropriate, HRQoL assessment-instruments with good psychometric properties (reliability and validity).

Generic instruments for children aged 10-15

The TNO/AZL Child Quality of Life Questionnaire (TACQOL) Child Form (CF) and Parent Form (PF) were used to assess generic aspects of HRQoL; see table 2 for subscales[19]. These questionnaires assess the occurrence of functional problems, and if such problems occur, the subsequent emotional reactions to these problems. Satisfactory psychometric properties (subscale Cronbach's α ranged from 0.73 to .082) of these instruments have been described by Verrips et al.[20].

The Linear analogue scale (LAS) measured self-perceived QoL (vertical line; 0 = worst, 100 = best imaginable QoL). The LAS has proven to be valid and reliable (Cronbach's α = 0.65) for the ConHD population[13].

Generic and cardiac-specific instruments for patients aged 16 and older

The SF-36 Health Survey (SF-36), a generic instrument, was used to assess subjective health status (table 3)[21]. Good reliability (mean Cronbach's α = 0.84) and validity has been reported for the Dutch version[22].

The Congenital Heart Disease-TNO/AZL Adult Quality of Life (CONHD-TAAQOL) assessed cardiac-specific aspects of HRQoL of youngsters with ConHD (table 4). Tests of its psychometric properties showed satisfactory results; Cronbach's α ranges from 0.77 to 0.82[1].

The Linear analogue scale (LAS) measured self-perceived QoL (see above).

Norm groups

For the ***TACQOL-CF***, the norm group consisted of 593 girls and 660 boys (n = 1253)[19]. For the TACQOL-PF no normative data were available.

The ***SF-36*** norm sample consisted of 1742 persons; 56 % men, age range: 16-40 years[22].

For the disease-specific ***CONHD-TAAQOL***, no normative data were available.

The ***LAS*** norm sample contained 600 participants aged 14 to 18.

Statistical analyses

Statistical analyses were based on the intention-to-treat principle. Because of small sample sizes and skewed distributions, exercise group changes *versus* control group changes were compared with Mann-Whitney tests ($p < .05$), also for diagnostic groups separately. Repeated measurements *within* the exercise group and control group were analyzed with Wilcoxon Signed Ranks Tests. Data are presented as median and inter quartile range (IQR). The effect size (*r)* for every result is calculated by the z-score divided by the square root of the number of observations.

Then data were split, based on baseline HRQoL tertiles, into 'low' (=1st tertile), and 'high' (=2nd and 3rd tertiles) and pre-post changes in the exercise group and control group were analyzed for baseline HRQoL groups separately. Because many children and parents obtained highest possible HRQoL scores, we also analyzed whether children and their

parents changed their maximal scoring after the exercise program and control period with McNemar tests.

Comparison with normative groups was calculated using Students' t tests (mean and standard deviations). Statistics were conducted using SPSS version 20.0 (IBM Corp., Armonk, NY).

RESULTS

Baseline characteristics

Three hundred and sixty-two eligible patients were contacted, of whom 93 (26%) finally participated, see figure 1 for flowchart. Two patients who were assessed at baseline re-

Table 1: Baseline demographic characteristics, cardio-respiratory fitness, and participation in sports activities

	Exercise group (n = 54)	Control group (n = 37)	P value
Demographic status			
Age in years	15.2 (12.6 -17.6)	15.4 (13.0 - 17.6)	0.77
Male	39 (72.2)	26 (70.3)	0.64
Congenital heart disease			0.70
Fontan	27 (50.0)	17 (45.9)	
Age at Fontan completion	3.0 (2.5 – 5.0)	3.0 (2.5 – 3.9)	0.66
Tetralogy of Fallot (ToF)	27 (50.0)	20 (54.1)	
Age at ToF operation	0.5 (0.4 – 1.1)	0.7 (0.5 – 0.9)	0.61
Social economic status			0.46
Low (1)	5 (9.3)	4 (10.8)	
Middle (2)	16 (29.6)	15 (40.5)	
High (3)	27 (50.0)	14 (37.8)	
Missing	6 (11.1)	4 (10.8)	
Cardio-respiratory fitness			
PeakVO_2 (% predicted)*	82.4 (17.0)	81.7 (20.0)	0.88
Peak load in Watt	143.6 (54.6)	147.0 (46.2)	0.76
Peak heart rate (bpm)	170.8 (20.4)	176.5 (18.6)	0.18
VE/VCO_2 slope	28.7 (5.3)	29.9 (6.8)	0.36
Participation in sports activities			0.35
Never	9 (17%)	8 (22%)	
1-4 hpw	33 (61%)	17 (46%)	
>5 hpw	12 (22%)	12 (32%)	

Demographic status and participation in sports activities: data are presented as number (percentage), age is presented as median (IQR). Cardio-respiratory fitness: data are presented as mean (standard deviation). * n = 11 missing values due to unsuccessful cardiopulmonary exercise test (respiratory exchange ratio (RER) < 1.0.) Hpw = hours per week, bpm = beats per minute.

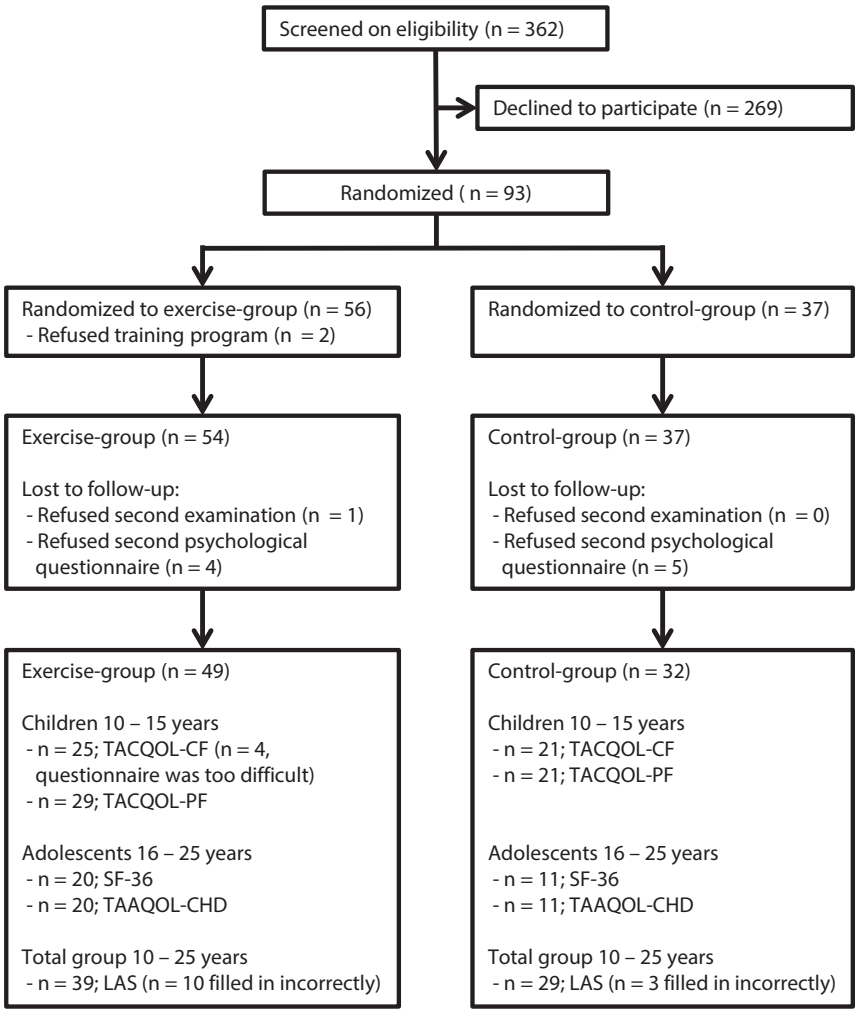


Figure 1: Enrollment

fused to participate in the rest of the study. Therefore, the final sample included 91 participants, median age: 15.4 years, 64/91 male, 47/91 ToF, 44/91 Fontan. Patients were recruited and followed-up between January 2010 and August 2012. No differences were found as to baseline characteristics between the exercise group and the control group; see table 1.

Exercise program adherence

Overall, 56 patients were randomized to the exercise group, of which 53 were followed-up after 3 months (see Figure 1). Of these patients in the exercise group, 37 already participated in sports activities in their daily lives. Median adherence to the exercise program was 89% (IQR = 79 – 100). According to a random sample of heart rate monitor

data, all exercise-patients heart rate ranges during the exercise-program were within the advised heart rate range.

Effects of an exercise program on quality of life

Children aged 10-15 years; TACQOL

Of the 32 children in the exercise program group and 22 children in the control group, respectively 25 and 21 children completed the TACQOL-CF (see table 2). Comparing pre-post change in the exercise group versus the control group, children in the exercise group improved more on cognitive functioning $z = -1.99$, $p < .05$, $r = .30$ than control children.

Table 2: Quality of Life questionnaire for children aged 10-15 years

TNO/AZL Child Quality of Life Questionnaire - Child Form (TACQOL-CF)					*p* value Δexercise vs Δcontrol	Normative data Child Form
	Exercise group (n = 25)		Control group (n = 21)			
Scales	Baseline	Follow-up	Baseline	Follow-up		
Pain and physical symptoms	25.0 (21.5 - 28.0)	26.0 (22.5 - 30.5)[b]	24.0 (19.5 - 27.0)	23.0 (20.0 - 29.0)	0.21	24.0 (20.0 - 28.0)
Motor functioning	30.0 (26.5 - 30.5)	30.0 (29.0 - 31.5)[a]	28.0 (26.0 - 31.5)	30.0 (26.5 - 32.0)	0.51	31.0 (29.0 - 32.0)
Cognitive functioning	27.0 (23.8 - 30.0)	29.0 (26.3 - 30.8)	30.0 (24.0 - 32.0)	29.0 (23.0 - 31.8)	0.05	28.0 (25.0 - 31.0)
Social functioning	32.0 (30.0 - 32.0)	32.0 (28.0 - 32.0)	32.0 (30.5 - 32.0)	32.0 (32.0 - 32.0)	0.45	32.0 (32.0 - 32.0)
Positive emotional functioning	15.0 (13.5 - 16.0)[b]	15.0 (11.5 - 16.0)	15.0 (11.5 - 16.0)	15.0 (12.3 - 16.0)	0.39	14.0 (11.0 - 15.0)
Negative emotional functioning	13.0 (10.0 - 16.0)	14.0 (12.0 - 16.0)[b]	13.0 (11.3 - 14.0)	14.0 (13.0 - 15.8)[a,b]	0.34	12.0 (10.0 - 14.0)

TNO/AZL Child Quality of Life Questionnaire - Parent Form (TACQOL-PF)					*p* value Δexercise vs Δcontrol
	Exercise group (n = 29)		Control group (n = 21)		
Scales	Baseline	Follow-up	Baseline	Follow-up	
Pain and physical symptoms	28.0 (23.0 - 29.0)	30.0 (27.5 - 32.0)[a]	27.0 (24.0 - 28.5)	30.0 (27.5 - 31.0)[a]	0.76
Motor functioning	28.0 (26.5 - 30.5)	32.0 (31.0 - 32.0)[a]	30.0 (27.0 - 32.0)	32.0 (30.0 - 32.0)[a]	0.21
Cognitive functioning	27.0 (22.5 - 30.0)	32.0 (29.0 - 32.0)[a]	29.0 (24.0 - 31.0)	32.0 (30.0 - 32.0)[a]	0.73
Social functioning	32.0 (28.0 - 32.0)	32.0 (32.0 - 32.0)[a]	32.0 (32.0 - 32.0)	32.0 (32.0 - 32.0)	0.04
Positive emotional functioning	16.0 (13.5 - 16.0)	15.0 (14.0 - 16.0)	15.0 (12.8 - 16.0)	15.5 (13.8 - 16.0)	0.39
Negative emotional functioning	13.0 (10.0 - 13.0)	13.0 (10.0 - 14.0)	11.0 (9.0 - 13.0)	13.0 (12.0 - 14.0)[a]	0.15

Data are presented as median (IQR), Δexercise indicates change in the exercise group during follow-up, and Δcontrol indicates change in the control group during follow-up. A higher score indicates a better quality of life. a) Significant different from pre-to-post using the Wilcoxon Signed Ranks Test; $p < 0.05$. b) Significant different from reference; $p < 0.05$.

Considering pre-post changes *within each group,* children in the exercise group themselves reported better motor functioning after the sports-intervention than before $z = -2.11$, $p < .05$, $r = .30$. Control children themselves scored higher, i.e. more favorable, on global negative functioning from pre-to post assessment, $z = -1.98$, $p < .05$, $r = .31$.

Twenty-nine parents in the exercise group and 21 parents in the control group completed the TACQOL-PF. Comparing pre-post changes, parents of children in the exercise group reported improved social functioning whereas parents of control children did not, $z = -2.07$, $p < .05$, $r = 0.30$.

Within both groups, parents reported improvements ($p < 0.01$, *r-range:* 0.44 - 0.53) on pain and physical symptoms, motor functioning, and cognitive functioning (table 2). Parents in the exercise group also reported improvements on social functioning ($p = 0.006$. $r = 0.36$).

Since the exercise program showed few significant effects on TACQOL-CF scores, further statistical analyses were performed for children who had low HRQoL scores at baseline. Children in the exercise group with low baseline scores on motor functioning and cognitive functioning, showed significant improvements on these scales, $z = -2.54$, $p < .05$, $r = .57$ and $z = -2.11$, $p < .05$, $r = .50$; see figure 2. They also seem to improve ($p = .068$, $r = .43$) on pain and physical symptoms. However, children in the control group, with 'low' baseline HRQoL, did not improve on these scales, they only improved on negative emotional functioning ($p < .05$, $z = .47$).

As to best possible scores, children in both groups did not obtain a higher number of maximal HRQoL scores from baseline to follow-up. On the other hand, parents in the exercise group reported a higher number of maximal scores for pain and physical symptoms ($p = 0.01$), motor functioning ($p < 0.01$), cognitive functioning ($p < 0.01$), and social functioning ($p < 0.02$) from pre- to post-assessment, whereas parents in the control group did not.

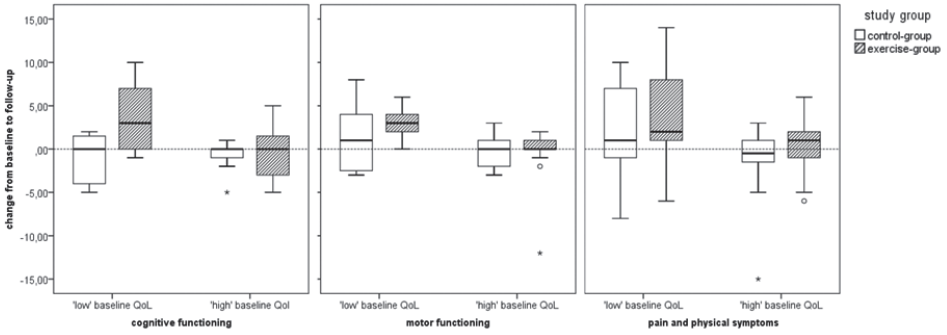


Figure 2: Differences in pre-post change in quality of life (QoL) between patients with low baseline QoL and high baseline QoL

Patients aged 16 - 25 years; SF-36

No significant differences in pre-post changes on the SF-36 were found between the exercise group and control group. Such pre-post changes were neither found *within* each group; table 3. Many patients obtained best possible SF-36 scores.

Patients aged 16-25 years; CONHD-TAAQOL

Patients in the exercise group and the control group did not show pre-post changes on the *symptoms* and the *worries* scale (table 3). Considering impact of cardiological surveillance, adolescents reported lower scores after the exercise program than they did before $z = -3.03$, $p < .01$, $r = .54$. Adolescents in the control group did not change on impact of cardiological surveillance. The median difference between the pre-post changes in the exercise group and the control group was 5.7 $p = 0.07$.

Total group 10 - 25 years

Changes in LAS scores did not differ between the exercise group and control group. No significant changes were found within each group.

Cardiac diagnosis and comparison with normative data

Cardiac diagnosis, Fontan versus Fallot, did not influence the effect of an exercise program on the generic TACQOL (child form nor parent form), SF-36 scales, disease-specific CONHD-TAAQOL, nor on the LAS.

Children aged 10-15 years; TACQOL

At baseline, self-reports of Fontan children did not differ from ToF children on any of the TACQOL-CF scales. Parents of Fontan children reported worse motor functioning than parents of ToF children, $z = -2.55$, $p < .02$, $r = .40$. No further differences between diagnostic groups were found on parent-scales.

Comparing baseline with normative data, Fontan children reported poorer motor functioning ($t(25) = -2{,}93$, $p < .01$) and less negative emotions ($t(25) = 2.56$, $p = .02$), whereas ToF children reported more positive emotions ($t(18) = 3.11$, $p < .01$).

Patients aged 16 - 25 years; Short-form 36

At baseline, Fontan patients reported worse physical functioning, $z = -2.14$, $p < .05$, $r = .38$ and lower general health, $z = -2.74$, $p < .01$, $r = .49$ than ToF patients (table 3).

Compared with normative data, Fontan patients and ToF patients reported less bodily pain (both $p < .01$), better social functioning (both $p < .01$), and less role limitations due to emotional problems (both $p < .05$) at baseline. Patients with ToF also reported less role limitations due to physical symptoms ($p < .05$) and better mental health ($p < .05$).

Table 3: Quality of Life questionnaires for adolescents aged 16-25

	Fontan (n = 9)	Tetralogy of Fallot (n = 22)	Normative data (16 - 40) Mean (SD)	Exercise group (n = 20)		Control group (n = 11)		*p* value Δexercise vs Δcontrol
	Baseline	Baseline		Baseline	Follow-up	Baseline	Follow-up	
Short-Form 36 (SF-36)								
Physical functioning	90.0 (65.0 - 95.0)[b]	97.5 (90.0 - 100.0)[b]	93.1 (11.8)	97.5 (80.0 - 100.0)	97.5 (86.3 - 100.0)	95.0 (90.0 - 100.0)	95.0 (90.0 - 100.0)	0.71
Bodily pain	100.00 (84.7 - 100.0)[c]	100.0 (89.8 - 100.0)[c]	80.9 (19.4)	100.0 (89.8 - 100.0) c	100.0 (89.8 - 100.0)[c]	100.00 (89.8 - 100.0)[d]	100.0 (79.6 - 100.0)[d]	0.96
General health	45.0 (40.0 - 70.0)[b, d]	75.0 (63.8 - 91.3)[b]	78.2 (17.3)	75.0(52.5 - 88.8)	70.0 (50.0 - 85.0)[d]	60.0 (60.0 - 80.0)	67.5 (56.3 - 78.8)	0.94
Vitality	75.0 (62.5 - 80.0)	75.0 (63.8 - 85.0)	70.7 (16.4)	75.0 (61.3 - 85.0)	70.00 (61.3 - 83.8)	75.0 (65.0 - 85.0)	70.0 (60.0 - 80.0)	0.56
Role limitations due to physical limitations	100.0 (87.5 - 100.0)	100.0 (100.0 - 100.0)	86.4 (27.6)	100.00 (100.0 - 100.0)[d]	100.0 (100.0 - 100.0)[c]	100.0 (100.0 - 100.0)[c]	100.0 (75.0 - 100.0)	0.16
Social functioning	100.0 (93.8 - 100.0)[c]	100.0 (100.0 - 100.0)[c]	87.8 (19.1)	100.0 (100.0 - 100.0)[c]	100.0 (87.5 - 100.0)	100.0 (87.5 - 100.0)	100.0 (100.0 - 100.0)[c]	0.09
Role limitations due to emotional problems	100.0 (100.0 - 100.0)[d]	100.0 (100.0 - 100.0)	85.4 (30.0)	100.0 (100.0 - 100.0)	100.0 (100.0 - 100.0)[c]	100.0 (100.0 - 100.0)[c]	100.0 (100.0 - 100.0)	0.72
Mental Health	80.0 (74.0 - 92.0)	88.0 (75.0 - 96.0)[d]	78.7 (15.2)	86.0 (76.0 - 95.0)[d]	86.0 (74.0 - 95.0)	84.0 (68.0 - 96.0)	80.0 (76.0 - 88.0)	0.65
The Congenital Heart Disease-TNO/AZL Adult Quality of Life (CONHD-TAAQOL)								
Symptoms	93.3 (88.9 - 97.8)	97.8 (92.8 - 100.0)		96.7 (91.1 - 100.0)	96.7 (90.0 - 100.0)	95.6 (91.1 - 97.8)	97.8 (95.6 - 100.0)	0.16
Impact Cardiological Surveillance*	85.7 (75.0 - 89.3)[b]	91.4 (85.7 - 97.9)[b]		91.4 (86.4 - 96.4)[a]	85.7 (80.7 - 88.6)[a]	85.7 (76.7 - 90.0)	85.7 (82.9 - 88.6)	0.07
Worries	90.0 (82.0 - 95.0)[b]	100.0 (90.0 - 100.0)[b]		99.0 (91.0 - 100.0)	98.0 (89.0 - 100.0)	90.0 (84.0 - 100.0)	94.0 (72.0 - 100.0)	0.67

Data are presented as median (inter quartile range), only reference data are presented as mean (standard deviation), a higher score indicates a better quality of life. a) significant different from pre-to-post using the Wilcoxon Signed Ranks Test; $p < 0.05$. b) significant differences between Fontan and tetralogy of Fallot adolescents using the Mann-Whitney Test ($p < .05$). c) significant different from reference group $p < 0.01$. d) significant different from reference group $p < 0.05$. * Comprise items like: In the last twelve months, have you had an ultrasound heart scan (MRI), when answered with yes, the subjective evaluation is assessed: how much did that bother you?

Furthermore, Fontan patients reported lower general health ($p < .05$), whereas ToF patients' general health was comparable to normal (table 3).

Patients 16 - 25 years; CONHD-TAAQOL

At baseline, Fontan adolescents reported more impact of cardiological surveillance, $z = -2.07$, $p < .05$, $r = .37$ and more worries, $z = -2.15$, $p < .05$, $r = 0.39$ than ToF adolescents, see table 3.

Total group 10 - 25 years; LAS

At baseline, Fontan children and adolescents reported comparable LAS scores (M*dn* = 80.0, IQR = 73.8 - 90.0) as ToF children and adolescents (M*dn* = 80.0, IQR = 70.0 - 85.0).

Exercise group and control group versus normative data

Children aged 10-15 years; TACQOL

At baseline, children in the exercise group reported more positive emotions ($p < .05$) than children from the general population (table 2). At follow-up, children in both study-groups reported less negative emotions than healthy peers (both $p < .05$). Moreover, children in the exercise group reported less pain and physical symptoms ($p < .05$).

Patients aged 16 - 25 years; SF-36

Comparing baseline with normative data, patients in the exercise group and control group reported less bodily pain ($p < .01$ and $p < .05$), less role limitations due to physical limitations ($p < .05$ and $p < .01$), and less role limitations due to emotional problems (both $p < .01$) (table 3). At baseline, adolescents in the exercise group also reported better social functioning ($p < .01$) and mental health ($p < .05$) than peers from the general population.

On post-assessment, patients in the exercise group reported sustained higher, more favorable scores for bodily pain ($p < .01$), role limitations due to physical limitations ($p < .01$), as well to emotional problems ($p < .01$) compared with normative data. In contrast, they reported lower general health ($p < .05$). Patients in the control group had sustained higher scores on bodily pain ($p < .05$).

Adolescents aged 14 - 18 years; LAS

At baseline, adolescents in the control group reported significantly better QoL at baseline than normative data, LAS means: 84.7 versus 76.7, $t(13) = 2.91$, $p = 0.012$. Adolescents in the exercise group did not report significantly better QoL at baseline compared with normative data: LAS means: 79.1 versus 76.7.

DISCUSSION

This study shows that children with ConHD between 10 and 15 years old, who participated in a standardized exercise program, improved on self-reported cognitive functioning. This is particularly true for those with low baseline HRQoL scores. In this subgroup, improvements were also noted on both cognitive and motor functioning and there was a trend towards improvements on pain and physical symptoms. Children in the control group with low baseline HRQoL scores did not improve on these scales.

According to parent-reports, children who participated in an exercise program improved on social functioning. However, almost all parents in both groups reported highest possible scores on social functioning; due to this ceiling effect of the questionnaire, this result is not very informative.

Analyses within groups showed that parents in both the exercise group and control group reported improvements on pain and physical symptoms, motor functioning and cognitive functioning. At follow-up, parents from both groups obtained more best possible scores for motor functioning and cognitive functioning. Possibly, the extensive examination, both medical and psychological, may have given parents a feeling of more safety and results may point towards a placebo effect.

The exercise program did not change QoL of adolescents and young adults, as shown by the generic SF-36 and LAS. This can be due to the fact that most adolescents had best possible scores at baseline. Beside this ceiling effect at baseline, they also reported better QoL compared with normative data. Presumably, these generic instruments are not sensitive enough to detect QoL changes in this patient population[1]. On the other hand, the ceiling effect was also noted on the disease-specific CONHD-TAAQOL. Higher scores might also be caused by selection bias; patients participated voluntarily to this study. These motivated patients have reported perhaps higher QoL scores than patients who did not participate. An exception was that adolescents in the exercise group reported more impact from cardiac surveillance at follow-up. These adolescents participated in an intensive 3-month program; therefore they may have perceived their cardiac surveillance at follow-up more as a burden, whereas adolescents in the control group did not.

As to cardiac diagnosis, ToF versus Fontan, we did not find any influence of diagnosis on HRQoL changes after the exercise program. Latal et al.[23] reviewed studies into QoL in children and adolescents with ConHD. They also found that cardiac diagnosis did not relate to QoL in a heterogeneous diagnostic sample. On the other hand, they found lower QoL scores in those children and adolescents with more complex malformations, such as single ventricle anatomy palliated with a Fontan operation. In line, adolescents/young adults with a Fontan circulation in our sample also reported lower baseline SF-36 physical functioning and general health compared with those with ToF. However, adolescents/young adults with a Fontan circulation in our sample did not

report greater HRQoL-changes in these or any other domains than adolescents/young adults with ToF.

To our knowledge, so far only three small studies into the influence of an exercise program on health status in ConHD children have been done[14, 15, 24]. The only intervention study[15] that used a similar standardized 12-week exercise program, did not find the improvements in parent-reported HRQoL that we found. Rhodes et al.[15] only showed non-significant improvements on all self-reported QoL domains after rehabilitation. They assessed QoL 1 year after the exercise program with a health status questionnaire. Health status, however, is another concept than health related quality of life, which we assessed[25]. In addition, their control group consisted of volunteers, who could not participate in the exercise program for geographical or social constraints. The difference with our findings may also relate to their smaller sample size. Finally, Rhodes et al. only included those children and adolescents with a peakVO2 of 80% predicted or less[15]. Mean baseline peakVO_2 percent predicted was 64.7% in their control group and 59.6% in their exercise group. In our sample, see Table 1, baseline mean peakVO_2 percent predicted was 82.4 % in the exercise group, and 81.7 % in the control group[15].

Two other intervention studies used a 3-day multi sports camp as intervention[14, 24] and reported improvements on several quality of life domains. However, findings are difficult to compare since the content of their intervention was very different, no control group was used, and their recall time frame of 3 days might have influenced their results.

Strengths and limitations

This is the first randomized controlled trial in this field with a standardized 12-week exercise program, an adequate control group, and multi-informant HRQoL instruments. We found improvements on two domains of HRQoL, in one age group. Possibly, if assessments would have been done with a more disease-specific questionnaire, instead of a generic one, and in a larger sample, we would have found better results.

As to limitations, though our sample size is larger than in the few previous studies, it is relatively small. Due to age-appropriate HRQoL questionnaires, our sample had to be divided into two groups, 10 – 15 years and 16 – 25 years. Therefore, sub-samples sizes were relatively small which may be associated with an increased type 2 error. Besides, a larger sample would have allowed us to investigate the differential impact of gender on the effects of an exercise program.

Regarding our design, those participants in the exercise group who already participated in sports activities themselves, were asked to participate in the exercise program for 2 sessions per week, in addition they were asked to monitor their own sports activities with a heart rate monitor. Those participants, who did not already participate in sports activities themselves, were asked to participate 3 times. On the other hand, participants in the control group were asked to continue their own regular daily activities (including

sports activities). Although we are aware of the interference with our 'controlled' design, in our opinion it would have been unethical to ask participants to discontinue their own sports activities.

Finally, a second, longer-term follow-up might have unraveled any sleeper-effects; i.e. long-term effects of interventions. Unfortunately, a second follow-up was not feasible.

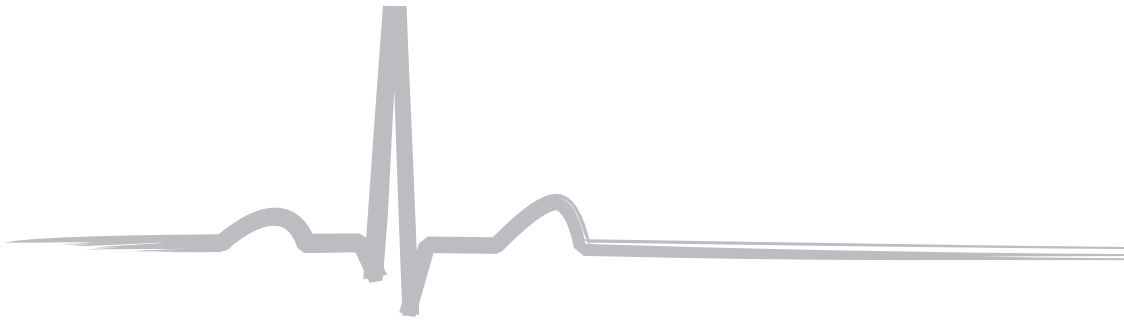
Conclusion

This exercise-program improved self-reported cognitive functioning and parent-reported social functioning in children aged 10 to 15. In contrast, this exercise-program did not improve the QoL of patients aged 16-25 years. This might be explained by their high self-reported baseline QoL. Another explanation is that a more age-appropriate sports-intervention, with more focus on obtaining autonomy and belonging to a peer-group, involving more 'normal' sports-participation with healthy peers, might have given better results.

REFERENCES

1. Kamphuis M, Zwinderman KH, Vogels T, Vliegen HW, Kamphuis RP, Ottenkamp J, Verloove-Vanhorick SP, Bruil J. A cardiac-specific health-related quality of life module for young adults with congenital heart disease: Development and validation. *Qual Life Res*. 2004;13:735-745
2. Jenkins PC, Chinnock RE, Jenkins KJ, Mahle WT, Mulla N, Sharkey AM, Flanagan MF. Decreased exercise performance with age in children with hypoplastic left heart syndrome. *J Pediatr*. 2008; 152:507-512
3. Moller P, Weitz M, Jensen KO, Dubowy KO, Furck AK, Scheewe J, Kramer HH, Uebing A. Exercise capacity of a contemporary cohort of children with hypoplastic left heart syndrome after staged palliation. *Eur J Cardiothorac Surg*. 2009;36:980-985
4. Takken T, Giardini A, Reybrouck T, Gewillig M, Hovels-Gurich HH, Longmuir PE, McCrindle BW, Paridon SM, Hager A. Recommendations for physical activity, recreation sport, and exercise training in paediatric patients with congenital heart disease: A report from the exercise, basic & translational research section of the european association of cardiovascular prevention and rehabilitation, the european congenital heart and lung exercise group, and the association for european paediatric cardiology. *Eur J Prev Cardiol*. 2012;19:1034-1065
5. Lunt D, Briffa T, Briffa NK, Ramsay J. Physical activity levels of adolescents with congenital heart disease. *Aust J Physiother*. 2003;49:43-50
6. Dulfer K, Helbing WA, Duppen N, Utens EM. Associations between exercise capacity, physical activity, and psychosocial functioning in children with congenital heart disease: A systematic review. *Eur J Prev Cardiol*. 2013
7. Cohen M, Mansoor D, Langut H, Lorber A. Quality of life, depressed mood, and self-esteem in adolescents with heart disease. *Psychosom Med*. 2007;69:313-318
8. Duppen N, Takken T, Hopman MT, Ten Harkel AD, Dulfer K, Utens EM, Helbing WA. Systematic review of the effects of physical exercise training programmes in children and young adults with congenital heart disease. *Int J Cardiol*. 2013;168:1779-1787
9. Tikkanen AU, Oyaga AR, Riano OA, Alvaro EM, Rhodes J. Paediatric cardiac rehabilitation in congenital heart disease: A systematic review. *Cardiol Young*. 2012;22:241-250
10. Minamisawa S, Nakazawa M, Momma K, Imai Y, Satomi G. Effect of aerobic training on exercise performance in patients after the fontan operation. *Am J Cardiol*. 2001;88:695-698
11. Fredriksen PM, Kahrs N, Blaasvaer S, Sigurdsen E, Gundersen O, Roeksund O, Norgaand G, Vik JT, Soerbye O, Ingjer E, Thaulow E. Effect of physical training in children and adolescents with congenital heart disease. *Cardiol Young*. 2000;10:107-114
12. Dua JS, Cooper AR, Fox KR, Graham Stuart A. Exercise training in adults with congenital heart disease: Feasibility and benefits. *Int J Cardiol*. 2010;138:196-205
13. Moons P, Van Deyk K, De Bleser L, Marquet K, Raes E, De Geest S, Budts W. Quality of life and health status in adults with congenital heart disease: A direct comparison with healthy counterparts. *Eur J Cardiovasc Prev Rehabil*. 2006;13:407-413
14. Moons P, Barrea C, Suys B, Ovaert C, Boshoff D, Eyskens B, Vandenrijn C, Sluysmans T. Improved perceived health status persists three months after a special sports camp for children with congenital heart disease. *Eur J Pediatr*. 2006;165:767-772
15. Rhodes J, Curran TJ, Camil L, Rabideau N, Fulton DR, Gauthier NS, Gauvreau K, Jenkins KJ. Sustained effects of cardiac rehabilitation in children with serious congenital heart disease. *Pediatrics*. 2006; 118:e586-593

16. Schulz KF, Altman DG, Moher D, Group C. Consort 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332
17. Utens EMWJ, Dulfer K. Rotterdams kwaliteit van leven interview. 2010
18. Occupational classification 2010 system. 2010
19. Vogels T, Bruil J, Koopman H, Fekkes M, Verrips GHW. Tacqol cf 12-15 manual *developed by leiden center for child healh and pediatrics lumc-tno*. 2004
20. Verrips GH, Vogels AG, den Ouden AL, Paneth N, Verloove-Vanhorick SP. Measuring health-related quality of life in adolescents: Agreement between raters and between methods of administration. *Child Care Health Dev*. 2000;26:457-469
21. Ware JE, Jr., Sherbourne CD. The mos 36-item short-form health survey (sf-36). I. Conceptual framework and item selection. *Med Care*. 1992;30:473-483
22. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E. Translation, validation, and norming of the dutch language version of the sf-36 health survey in community and chronic disease populations. *J Clin Epidemiol*. 1998;51:1055-1068
23. Latal B, Helfricht S, Fischer JE, Bauersfeld U, Landolt MA. Psychological adjustment and quality of life in children and adolescents following open-heart surgery for congenital heart disease: A systematic review. *BMC Pediatr*. 2009;9:6
24. Moons P, Barrea C, De Wolf D, Gewillig M, Massin M, Mertens L, Ovaert C, Suys B, Sluysmans T. Changes in perceived health of children with congenital heart disease after attending a special sports camp. *Pediatr Cardiol*. 2006;27:67-72
25. Moons P, Budts W, De Geest S. Critique on the conceptualisation of quality of life: A review and evaluation of different conceptual approaches. *Int J Nurs Stud*. 2006;43:891-901



Chapter 9

Parental mental health moderates the efficacy of exercise training on health-related quality of life in adolescents with congenital heart disease.

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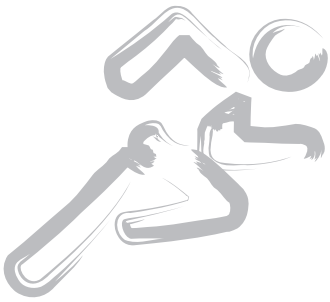

ABSTRACT

Background: To evaluate the moderating influence of parental variables on changes in health-related quality of life (HRQoL) in adolescents with Tetralogy of Fallot (ToF) or a Fontan circulation after participation in standardized exercise training.

Design: A multicenter randomized controlled trail in which 56 patients, aged 10 to 15, were randomly allocated (stratified by age, gender and congenital heart disease) to a 12-week period with either: a) 3 times per week standardized exercise training or b) care-as-usual (randomization ratio 2:1). Adolescents and their parents filled in online questionnaires at baseline and at 12 week follow-up.

Methods: In this randomized controlled trail, primary analyses involved influence of parental mental health and parental social support for exercise on changes in the TNO/AZL Child Quality of Life Questionnaire Child Form at follow-up. Secondary analyses concerned comparing levels of parental characteristics with normative data.

Results: Compared with controls, adolescents in the exercise group reported a decrease in social functioning when their parents had more anxiety/insomnia or severe depression themselves. Adolescents also reported a decrease in social functioning when their parents showed poorer overall mental health themselves.

Parents reported comparable or even better mental health compared with normative data.

Conclusions: The effect of a standardized exercise program on HRQoL changes in adolescents with ToF or a Fontan circulation is moderated by parental mental health, more specifically by parental anxiety/insomnia and severe depression. NTR2731 (trialregister.nl)

INTRODUCTION

Due to advances in medical care over the past 30 years, survival rates of children with congenital heart disease (ConHD) have increased enormously. Nowadays, 85% of these children survive into adulthood[1]. After surgical treatment, children with ConHD may experience limitations such as a reduced exercise capacity[2], lower physical activity levels[3], and also impaired health-related quality of life (HRQoL)[4, 5].

Exercise training may improve exercise capacity of children with ConHD[6]. However, despite well-known beneficial effects of physical activity, children with ConHD are less vigorously active than their healthy peers[3, 7]. Parental anxiety and overprotection may hamper participation of children with ConHD in physical activities[8, 9]. In adolescents from the general population, parental support for exercise is positively related to moderate-to-vigorous physical activity[10, 11].

Parental overprotectiveness towards participation in physical activity regarding their ConHD child may be the result of parental psychological factors such as: feelings of loss of control, uncertain long-term prognosis, and negative past experiences[9]. Besides, parental mental health and parental worries also appeared to be strong predictors for children's emotional adjustment, whereas disease severity and surgical factors were not[12, 13]. Berant et al.[14] found that a maternal avoidant attachment style in the period of ConHD diagnosis was associated with emotional problems and poor self-image in the children 7 years later.

Summarizing, previous studies showed that if parents are not anxious (regarding sports) and if they support their child regarding sports, this will have a beneficial influence on their child's sports participation. To our knowledge, the role of parental variables on psychological effects of an exercise-program in children with ConHD has never been studied before. These parental variables are moderators since they identify on whom and under what circumstances the intervention has different effects[15]. Our hypothesis is that parental variables such as parental mental health and parental social support for exercise may have a moderating effect of a standardized 12-week exercise training program on HRQoL of children with ConHD.

The present study is a multi-center, prospective, randomized controlled, intervention study into the effect of standardized exercise training in a cohort of children and adolescents, aged 10-15 years, with either tetralogy of Fallot (ToF) or a Fontan circulation. Two-third of both ToF respectively Fontan children were randomized to an aerobic exercise training program; the remaining one-third served as controls and received care-as-usual.

This study's aims concern:

- What is the moderating role of parental mental health and parental social support towards exercise on the effect of a 12-week exercise program versus care-as-usual in adolescents, aged 10-15, with ToF or a Fontan circulation on HRQoL scores, from pre-to post assessment?

- What is the level of parental mental health and social support in the exercise group and in the control group at follow-up, compared with normative data?

METHODS

Participants

Between January 2010 and August 2012, 93 patients aged 10 to 25 who underwent surgery for either Tetralogy of Fallot or single-ventricle physiology (treated with the Fontan operation) were included. Patients were treated at one of the 5 participating centers of pediatric cardiology in the Netherlands: Academic Medical Center Amsterdam, Erasmus Medical Center Rotterdam, Leiden University Medical Center, University Medical Center St Radboud, and University Medical Center Utrecht.

Excluded were patients with: contra-indications for exercise, mental retardation, standard contra-indications for MRI, or a ventricular outflow obstruction (peak Doppler gradient > 60 mm Hg). Since the focus of this study was on parental moderators, and due to the age-range of the selected questionnaires, adolescents and young adults aged 16 and older were excluded.

Randomization

After informed consent had been obtained, patients received an anonymous study code and were invited for medical and psychological *baseline* assessments. Thereafter, a 'blind' independent researcher allocated the patients to the exercise program or the control group (ratio 2:1) according to stratified randomization. All participants were stratified into groups by age, gender, and cardiac diagnosis. Each first and second patient in the stratification-group (e.g. age-group 10-12, boys, ToF) were randomized through envelopes. The randomization of the third patient in the stratification-group was dependent of the previous two randomizations.

Intervention

The standardized exercise training-program consisted of 3 training sessions of 1 hour per week, during a 3-month period. The training-program consisted of 10 minutes warming-up, 40 minutes aerobic dynamic cardiovascular training (60-70% of heart rate reserve, based on baseline ergometer-test), and 10 minutes cooling down. Children who already participated in other sports activities participated in 2 training sessions per week. The standardized program was performed group-wise, under supervision of a trained physiotherapist in local physiotherapy centers throughout the Netherlands. The same researcher (ND) visited all participating physiotherapists prior to the start of the program and visited them thereafter when needed, to ensure standardized implemen-

tation of the training program. The control group continued their normal daily live and received regular medical care.

Assessment procedure

The research protocol was approved by the ethics-committee review boards of all 5 medical centers. All eligible patients and their parents were approached uniformly through a patient-information letter and completed the same psychological instruments at 2 points in time. The baseline psychological assessment, a *web-based* questionnaire and a semi-structured interview by phone, took place no longer than 2 months before the start of the exercise program, and 1-3 days before the baseline cardiac assessment in the hospital. The second psychological assessment was performed no later than one month after completion of the exercise program, and no more than 2 weeks after the second cardiac assessment in the medical center. Assessments for control groups were performed at comparable points.

Outcome measure

The primary outcome measure was the TNO/AZL Child Quality of Life Questionnaire Child Form (TACQOL-CF), a generic instrument that measures self-reported general aspects of HRQoL in children[16]. The TACQOL-CF assesses the occurrence of functional problems, and if such problems occur, subsequently negative emotional reactions are assessed. The TACQOL-CF consists of 6 scales (56 items): 1) pain and physical symptoms, 2) motor functioning, 3) cognitive functioning, 4) social functioning, 5) global positive emotional functioning and 6) global negative emotional functioning. The satisfactory psychometric properties have been described by Verrips[17].

Parental moderators

Parental mental health was assessed with the 28-item Dutch version of the *General Health Questionnaire-28 (GHQ-28)*[18, 19]. The reliability and validity of the Dutch GHQ-28 were satisfactory[19]. The GHQ-28 consists of one total GHQ-score and four scales: somatic symptoms, anxiety/insomnia, social dysfunction, and severe depression. The GHQ normative group consisted of 485 participants from the general population (45% male), aged 18 years and older from the general population[19].

Parental social support for exercise was assessed with the Dutch version of the *Social Support for Diet and Exercise*[20, 21] which consists of 3 scales (18 items). For this study we used one scale: Family support for Exercise Habits Scale: Participation and Involvement (SSE). No normative data for adolescents were available.

Statistical analysis

This randomized controlled trial is designed according to the CONSORT guidelines[22] with analyses conform the intention-to-treat principle. Baseline scores of the TACQOL-CF, GHQ-28, and SSE for participants with follow-up assessment and those lost to follow-up were compared with Mann-Whitney tests ($p < 0.05$).

First, correlations between pre-post changes for TACQOL-CF subscales and baseline GHQ-scales and SSE were calculated. Then, we used general linear models, in which the repeated measures of TACQOL-CF baseline and follow-up scales were regressed on time, study group, and parental moderators. We tested moderations of parental variables through interactions of those parental variables with study group[15]. For each TACQOL-CF scale, univariate regressions were tested against a significance of $p < .008$ (Bonferroni correction, $p = 0.05/ 6$ parental moderators), then β with standard errors were reported. After this, we calculated correlations between parental moderators to identify collinearity. Finally, and only if parental moderators' cross-correlations were not too high (>.50)[23], all significant moderators of a specific TACQOL-CF scale were combined in a final repeated measures model to control for each of the other significant predictors.

Comparison with normative groups were calculated using Students' t tests ($p < 0.05$). Data were analyzed using SPSS version 20.0.

RESULTS

Preliminary Analyses

Fifty-six adolescents were randomized to the exercise group or the control group, see Figure 1. Two adolescents dropped out directly after the baseline assessment. During follow-up, 1 participant was lost. In case of 12 adolescents data were missing on the main outcome (7 patients refused to fill in questionnaire, for 1 patient the questionnaire was too difficult) or on parental predictor variables (n = 4); the complete cases sample consisted of data on 41 adolescents and their parent.

No differences were found on baseline TACQOL-CF, GHQ-28, and SSE scores between participants with a follow-up assessment and those lost to follow-up.

At baseline, adolescents in the exercise group did not differ from those in the control group as to baseline demographic characteristics, see Table 1, nor on TACQOL-CF-scores. Parents in the exercise group and those in the control group did not differ on GHQ scores and SSE scores on baseline, see supplemental Table 4.

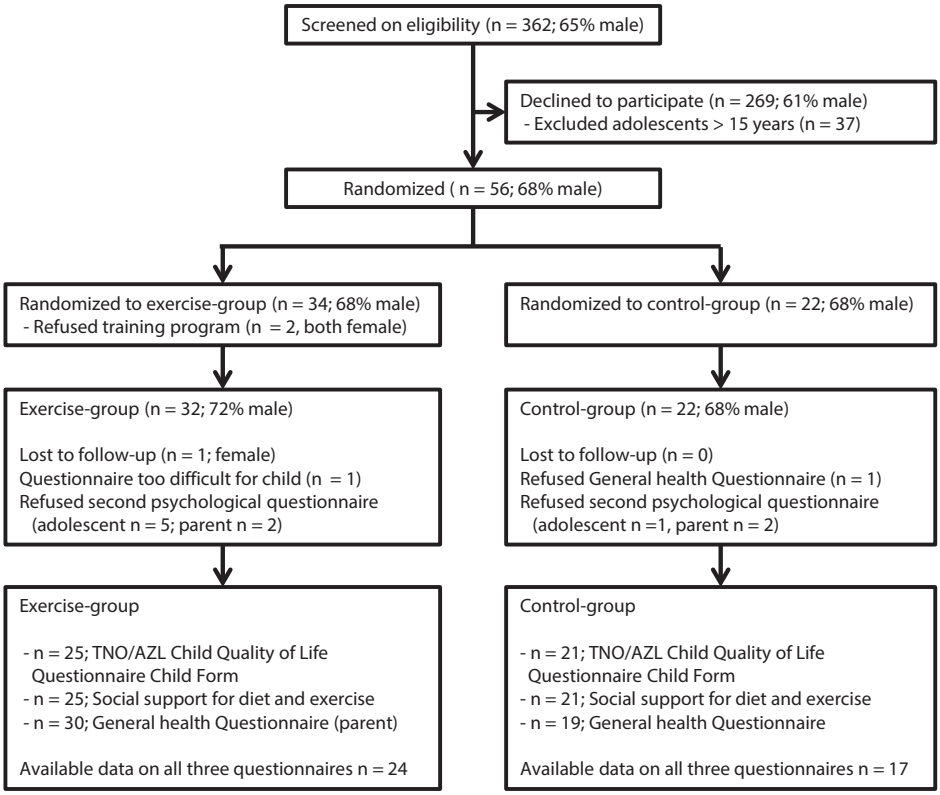

Figure 1: Enrollment

Table 1: Baseline demographic characteristics

	Exercise group n = 24	Control group n = 17
Child		
Age in years	13.3 (12.0 - 15.0)	13.2 (11.9 - 15.3)
Male	17 (70.8)	12 (70.6)
Tetralogy of Fallot	11 (45.8)	7 (41.2)
Fontan circulation	13 (54.2)	10 (58.8)
Parents		
Father	6 (25.0)	5 (29.4)
Age father	46.0 (42.0 - 49.0)	46.0 (41.8 - 51.5)
Mother	18 (75.0)	12 (70.6)
Age mother	43.5 (40.3 - 47.0)	43.5 (41.3 -46.8)
Social economic status		
Low (1)	4 (16.7)	1 (5.9)
Middle (2)	7 (29.2)	8 (47.1)
High (3)	13 (54.2)	8 (47.1)

Data are presented as number (percentage), only age is presented as median (inter quartile range).

Moderating influence of parental mental health and social support on HRQoL changes

Parental mental health

Correlations between pre-post changes in TACQOL-CF and baseline parental mental health (GHQ) and parental social support (SSE) scores were divided by exercise group and control group, see Table 2. In the exercise group, six correlations were significant, whereas in the control group no significant correlations were found. In summary, higher parental mental health in the exercise group was associated with less HRQoL changes in adolescents.

In univariate repeated measures analyses, moderations in pre-post changes in TAC-QOL scales were tested through interactions between parental mental health scales and study group (exercise group versus control group). A higher total GHQ score at baseline was associated with a pre-post decrease in social functioning in the exercise group, compared with the control group, $F(1,37) = 11.2$, $p = .002$, see figure 2. More parental severe depression and parental anxiety/insomnia at baseline, were also associated with a pre-post decrease in social functioning in the exercise group, compared with the control group (respectively $F(1,37) = 11.8$, $p = .001$ and $F(1,37) = 10.5$, $p = .003$).

According to Cohen's criteria[23], large correlations were found between total GHQ score and anxiety/insomnia $r = 0.71$, $p < .001$, total GHQ score and severe depression, $r = 0.73$, $p < .001$, and severe depressions and anxiety/insomnia, $r = 0.50$, $p < .005$. Therefore, no final model with all significant parental moderators was analyzed.

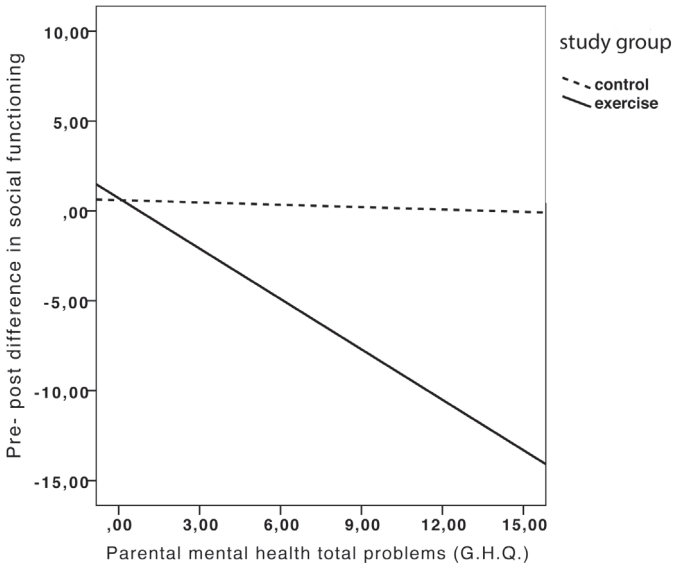

Figure 2: Associations between pre-post change in social functioning and parental mental health total problem score, split for study group

Table 2: Correlations between pre-post[1] changes in child-reported health related quality of life, and baseline parental mental health or parental social support

	Baseline General Health Questionnaire										Social support for exercise	
	Somatic symptoms		Anxiety/insomnia		Social dysfunction		Severe depression		Total score			
Change in TACQOL-CF	Exercise	Control	Exercise	Control	Exercise	Control	Exercise	Control	Exercise	Control	Exercise	Control
Pain and physical symptoms	−.10	−.05	.25	−.12	.00	−.21	.27	−.01	−.05	−.07	.14	.06
Motor functioning	.23	−.34	−.05	.21	.16	.16	−.08	−.05	.00	.04	.26	.17
Cognitive functioning	−.03	.35	−.07	.21	.05	−.07	−.22	.27	−.66 *	−.09	−.05	.02
Social functioning	−.40	−.18	−.69 *	−.16	−.25	−.08	−.58 *	−.11	−.15	−.05	−.20	.39
Positive emotional functioning	−.37	−.19	−.24	.14	−.43 *	−.41	−.31	−.23	−.59 *	−.20	−.20	.19
Negative emotional functioning	−.41 *	−.23	−.36	−.20	−.15	.12	−.19	−.47	−.39	−.39	−.39	−.21

1. pre-post changes = differences between baseline and follow-up assessment, TACQOL-CF= TNO/AZL Child Quality of Life Questionnaire Child Form, * $p < 0.05$.

Table 3: Gender-specific baseline means of parental mental health and parental social support for exercise

	Mothers (n = 30)	Norm female	Fathers (n = 11)	Norm male
General Health Questionnaire-28 (GHQ-28)				
Somatic symptoms	4.3 (3.3) a	6.7	4.7 (3.0)	5.4
Anxiety/insomnia	3.7 (3.2) a	6.0	5.0 (4.7)	5.5
Social dysfunction	7.5 (1.0) a	6.9	6.8 (0.6)	7.1
Severe depression	1.1 (2.8)	1.6	1.2 (3.3)	1.5
Total score	2.6 (3.6) a	5.5	2.5 (4.6)	3.9
Social support for Exercise (SSE)				
Family support	32.8 (11.3)		30.1 (9.2)	

Data are presented as mean (standard deviation).GHQ-28; a higher score indicates worse General Health, SSE: a higher score indicates more social support. a) Significantly different from norm females, b) Significantly different from norm males.

Parental social support for exercise

No significant correlations between changes in child-reported HRQoL and baseline parental social support for exercise were found, see Table 2.

In univariate regressions, no pre-post changes in HRQoL were significantly associated with baseline parental social support for exercise.

Comparison parental mental health with normative groups

Parental mental health

ConHD-mothers reported less somatic symptoms, anxiety/insomnia, and less symptoms on the total GHQ than normative females, see Table 3. On social dysfunction, they reported more complaints. Further no differences were found, nor for mothers, nor for fathers.

DISCUSSION

This is the first study showing that parental mental health moderated the effect of a 12-week standardized exercise program on HRQoL in adolescents with ToF or a Fontan circulation. Compared with controls, adolescents in the exercise group reported a pre-post decrease in social functioning when their parents themselves reported more mental health problems (total GHQ) and more specifically: more parental anxiety/insomnia and severe depression.

Compared to normative females, ConHD-mothers showed similar or even better outcomes on mental health (GHQ). Only on social dysfunction, they reported more complaints. Previous studies into parental mental health have also shown that, on the long-term, parents of somatically ill children reported comparable or even better mental health compared with parents from the general population[24-27]. The phenomenon that parents with a chronically ill child change their internal standards towards their HRQoL is described in previous studies as response shift or post-traumatic growth[28, 29]. Since mothers filled in most questionnaires in our study, it was not possible to compare the small sample of fathers in our sample adequately with those from the general population.

Although parents in our sample reported better mental health than normative groups, adolescents whose parents' overall mental health was relatively worse, reported a pre-post decrease in social functioning after the exercise program, compared with controls. They also reported a pre-post decrease in social functioning when their parents had worse outcomes on severe depression and anxiety/insomnia. Social functioning was assessed as interaction with peers containing the following items: being able to play or

talk happily with other children, being able to stand up for myself with other children, other children asked me to play with them, and I felt at ease with other children. An implied aim of group-wise exercise training was also to improve social functioning. A possible mechanism behind this unexpected finding might be that parents who are more anxious in general could also be more anxious specifically towards sports participation of their ConHD child in normal life[9]. Therefore, these children might have much lesser experience as to sporting and exercising in a group format compared with peers. Once these children participated in the exercise program, they might have been confronted with and gained insight into their impaired social functioning in this specific sports environment. Furthermore, their anxious parents might have shown (perhaps nonverbally) their anxiety during the exercise program, in front of the other children and parents. This might have hampered the ConHD children in their social interactions with other children. Therefore, they may have scored their social functioning after the exercise program as worse compared with their baseline social functioning. Overall, parental mental health problems may hamper the expected improvements, or may even establish a decrease, in the social aspect of group-wise exercise training.

Overall, parental moderators had an influence only on psychosocial HRQoL. Majnemer et al.[30] also found that higher levels of parental stress were associated with lower psychosocial well-being in their child. Furthermore, parental stress and parental psychopathology were also associated with poorer child-reported behavioral and social adjustment[31] and both physical and psychosocial HRQoL[32] in pediatric cancer survivors. In our study, parental moderators did not predict changes in physical HRQoL subscales. We expect that medical and physical parameters will predict changes in physical HRQoL better[30, 33].

As to the associations between parental social support and child-reported HRQoL, some studies[34, 35] reported positive correlations. In contrast, we found no associations. A possible explanation is that the two other studies assessed parent-reported social support, whereas we assessed social support for exercise reported by the adolescents themselves. Moreover, the other studies assessed generic social support, whereas we used a specific questionnaire aimed at family support for exercise habits, sports participation and involvement.

Limitations

Though our RCT-sample is large for this field in research, for statistical analysis it is relatively small, this may have increased type 2 error. Moreover, selection bias, such as sampling bias, may have occurred. Twenty-six percent of the eligible adolescents with ToF or a Fontan circulation participated in our RCT.

Clinical implications

This is the first study showing that parental mental health is a significant moderator for effects of exercise training on HRQoL in their children. Thus, this factor should be taken into account and targeted in clinical practice. Clinicians should communicate and propagate physical activity information and knowledge[36] with depressed and anxious parents in a sensitive way. For parents with mental health problems, it is important that adequate help and, if needed, referral is arranged.

Considering our findings, this may have a beneficial effect on HRQoL outcomes of adolescents taking part in exercise training.

Conclusions

Adolescents with ToF or a Fontan circulation with parents who showed more severe depression and anxiety/insomnia, or who had poorer overall mental health, showed a pre-post decrease in social functioning after exercise training. This is the first study showing that parental mental health is a significant moderator for psychological success of exercise training.

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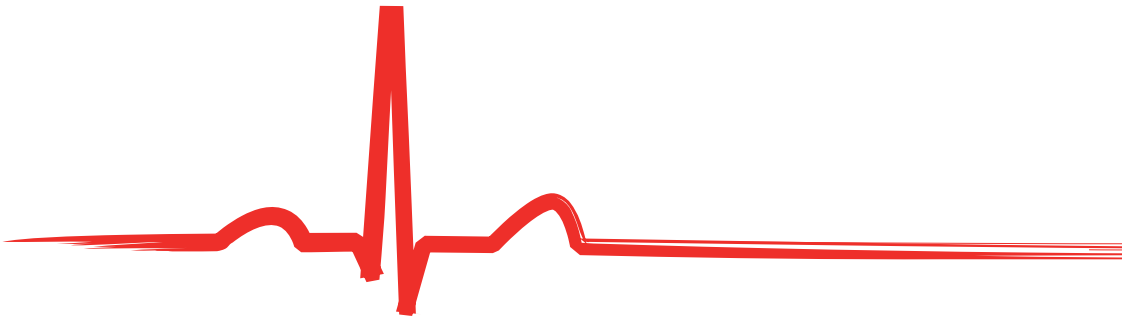
REFERENCES

1. Kamphuis M, Zwinderman KH, Vogels T, Vliegen HW, Kamphuis RP, Ottenkamp J, Verloove-Vanhorick SP, Bruil J. A cardiac-specific health-related quality of life module for young adults with congenital heart disease: Development and validation. *Qual Life Res*. 2004;13:735-745
2. Moller P, Weitz M, Jensen KO, Dubowy KO, Furck AK, Scheewe J, Kramer HH, Uebing A. Exercise capacity of a contemporary cohort of children with hypoplastic left heart syndrome after staged palliation. *Eur J Cardiothorac Surg*. 2009;36:980-985
3. McCrindle BW, Williams RV, Mital S, Clark BJ, Russell JL, Klein G, Eisenmann JC. Physical activity levels in children and adolescents are reduced after the fontan procedure, independent of exercise capacity, and are associated with lower perceived general health. *Arch Dis Child*. 2007;92: 509-514
4. Latal B, Helfricht S, Fischer JE, Bauersfeld U, Landolt MA. Psychological adjustment and quality of life in children and adolescents following open-heart surgery for congenital heart disease: A systematic review. *BMC Pediatr*. 2009;9:6
5. Spijkerboer AW, Utens EM, De Koning WB, Bogers AJ, Helbing WA, Verhulst FC. Health-related quality of life in children and adolescents after invasive treatment for congenital heart disease. *Qual Life Res*. 2006;15:663-673
6. Duppen N, Takken T, Hopman MT, Ten Harkel AD, Dulfer K, Utens EM, Helbing WA. Systematic review of the effects of physical exercise training programmes in children and young adults with congenital heart disease. *Int J Cardiol*. 2013;168:1779-1787
7. Lunt D, Briffa T, Briffa NK, Ramsay J. Physical activity levels of adolescents with congenital heart disease. *Aust J Physiother*. 2003;49:43-50
8. Bar-Mor G, Bar-Tal Y, Krulik T, Zeevi B. Self-efficacy and physical activity in adolescents with trivial, mild, or moderate congenital cardiac malformations. *Cardiol Young*. 2000;10:561-566
9. Moola F, Faulkner GE, Kirsh JA, Kilburn J. Physical activity and sport participation in youth with congenital heart disease: Perceptions of children and parents. *Adapt Phys Activ Q*. 2008;25:49-70
10. Ornelas IJ, Perreira KM, Ayala GX. Parental influences on adolescent physical activity: A longitudinal study. *Int J Behav Nutr Phys Act*. 2007;4:3
11. Gustafson SL, Rhodes RE. Parental correlates of physical activity in children and early adolescents. *Sports Med*. 2006;36:79-97
12. McCusker CG, Doherty NN, Molloy B, Casey F, Rooney N, Mulholland C, Sands A, Craig B, Stewart M. Determinants of neuropsychological and behavioural outcomes in early childhood survivors of congenital heart disease. *Arch Dis Child*. 2007;92:137-141
13. Lawoko S, Soares JJ. Psychosocial morbidity among parents of children with congenital heart disease: A prospective longitudinal study. *Heart Lung*. 2006;35:301-314
14. Berant E, Mikulincer M, Shaver PR. Mothers' attachment style, their mental health, and their children's emotional vulnerabilities: A 7-year study of children with congenital heart disease. *J Pers*. 2008;76:31-65
15. Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. *Arch Gen Psychiatry*. 2002;59:877-883
16. Vogels T, Bruil J, Koopman H, Fekkes M, Verrips GHW. Tacqol cf 12-15 manual *developed by leiden center for child healh and pediatrics lumc-tno*. 2004
17. Verrips GH, Vogels AG, den Ouden AL, Paneth N, Verloove-Vanhorick SP. Measuring health-related quality of life in adolescents: Agreement between raters and between methods of administration. *Child Care Health Dev*. 2000;26:457-469

18. Goldberg DP. *The detection of psychiatric illness by questionnaire* London: Oxford University Press; 1972.
19. Koeter MWJ, Ormel J. *General health questionnaire. Dutch version.* Lisse: Swets & Zeitlinger; 1992.
20. Sallis JF, Grossman RM, Pinski RB, Patterson TL, Nader PR. The development of scales to measure social support for diet and exercise behaviors. *Prev Med*. 1987;16:825-836
21. Stevens M, Bakker van Dijk A, de Greef MH, Lemmink KA, Rispens P. A dutch version of the social support for exercise behaviors scale. *Percept Mot Skills*. 2000;90:771-774
22. Schulz KF, Altman DG, Moher D, Group C. Consort 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332
23. Cohen J. A power primer. *Psychol Bull*. 1992;112:155-159
24. Utens EM, Versluis-Den Bieman HJ, Witsenburg M, Bogers AJ, Hess J, Verhulst FC. Does age at the time of elective cardiac surgery or catheter intervention in children influence the longitudinal development of psychological distress and styles of coping of parents? *Cardiol Young*. 2002;12:524-530
25. Wray J, Sensky T. Psychological functioning in parents of children undergoing elective cardiac surgery. *Cardiol Young*. 2004;14:131-139
26. Spijkerboer AW, Helbing WA, Bogers AJ, Van Domburg RT, Verhulst FC, Utens EM. Long-term psychological distress, and styles of coping, in parents of children and adolescents who underwent invasive treatment for congenital cardiac disease. *Cardiol Young*. 2007;17:638-645
27. Vrijmoet-Wiersma CM, Ottenkamp J, van Roozendaal M, Grootenhuis MA, Koopman HM. A multicentric study of disease-related stress, and perceived vulnerability, in parents of children with congenital cardiac disease. *Cardiol Young*. 2009;19:608-614
28. Rapkin BD, Schwartz CE. Toward a theoretical model of quality-of-life appraisal: Implications of findings from studies of response shift. *Health Qual Life Outcomes*. 2004;2:14
29. Colville G, Cream P. Post-traumatic growth in parents after a child's admission to intensive care: Maybe nietzsche was right? *Intensive Care Med*. 2009;35:919-923
30. Majnemer A, Limperopoulos C, Shevell M, Rohlicek C, Rosenblatt B, Tchervenkov C. Health and well-being of children with congenital cardiac malformations, and their families, following open-heart surgery. *Cardiol Young*. 2006;16:157-164
31. Colletti CJ, Wolfe-Christensen C, Carpentier MY, Page MC, McNall-Knapp RY, Meyer WH, Chaney JM, Mullins LL. The relationship of parental overprotection, perceived vulnerability, and parenting stress to behavioral, emotional, and social adjustment in children with cancer. *Pediatr Blood Cancer*. 2008;51:269-274
32. Yagc-Kupeli B, Akyuz C, Kupeli S, Buyukpamukcu M. Health-related quality of life in pediatric cancer survivors: A multifactorial assessment including parental factors. *J Pediatr Hematol Oncol*. 2012;34:194-199
33. Dulfer K, Helbing WA, Duppen N, Utens EM. Associations between exercise capacity, physical activity, and psychosocial functioning in children with congenital heart disease: A systematic review. *Eur J Prev Cardiol*. 2014;21:1200-1215
34. Wang Q, Hay M, Clarke D, Menahem S. Associations between knowledge of disease, depression and anxiety, social support, sense of coherence and optimism with health-related quality of life in an ambulatory sample of adolescents with heart disease. *Cardiol Young*. 2013:1-8
35. Luyckx K, Goossens E, Rassart J, Apers S, Vanhalst J, Moons P. Parental support, internalizing symptoms, perceived health status, and quality of life in adolescents with congenital heart disease: Influences and reciprocal effects. J Behav Med. 2012;37:145-55
36. Moola F, Fusco C, Kirsh JA. The perceptions of caregivers toward physical activity and health in youth with congenital heart disease. *Qual Health Res*. 2011;21:278-291



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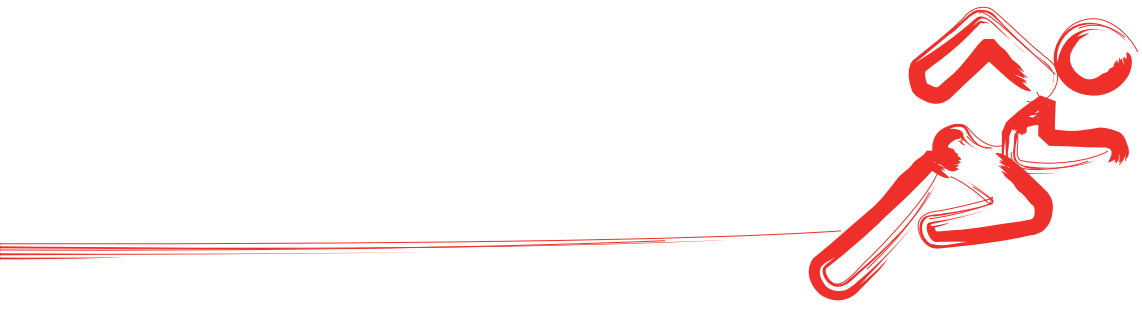
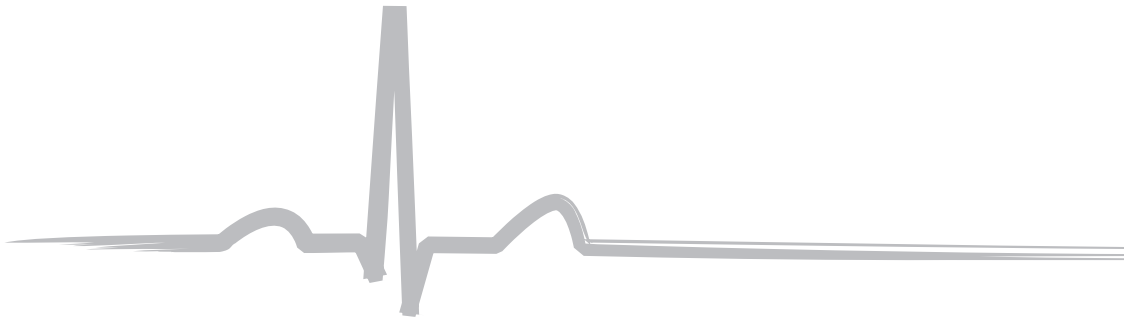
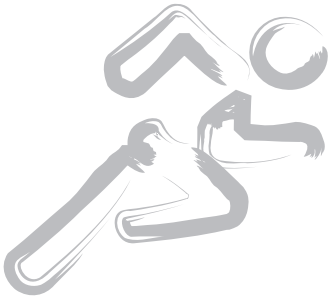




Chapter 10

General Discussion



The aim of the TOFFIT trial was to investigate if a standardized aerobic dynamic exercise training program is safe, effective and if it would improve quality of life in children and young adults with corrected tetralogy of Fallot and Fontan circulation.

In this chapter we will give an overview of our most relevant findings. We will first of all discuss if the training program was safe, then if it was effective and last of all if it improved the quality of life. We will describe the clinical implications as well as the strengths and limitations of our randomized controlled trial. This chapter concludes with suggestions for future research.

IS A STANDARDIZED AEROBIC DYNAMIC EXERCISE TRAINING PROGRAM SAFE?

To assess the safety of the exercise training program we examined the occurrence of adverse events, the remodeling of the heart, the wall shear stress in the pulmonary artery of Fontan patients and the neurohormonal status.

Adverse events: sudden cardiac death

The incidence of sudden cardiac death is 1 to 3 per 100 000 athletes. The incidence rises as the level of competition increases. Although the incidence is low, sudden cardiac death generates much public attention. In young athletes sudden cardiac death is often the first clinical manifestation of an underlying cardiovascular disorder[1].

Parents, teachers and physical activity coaches often fear sudden cardiac death when confronted with ConHD patients wishing to engage in physical activity. This is despite important differences in underlying pathology between young athletes who die suddenly and children with ConHD[2].

Exercise training studies that have included patients with ConHD did not report any case of sudden cardiac death (**chapter 2,5**). It should be acknowledged that most studies in ConHD populations excluded patients with sustained arrhythmias and severe obstruction to ventricular outflow. These are generally accepted contra-indications to perform physical exercise in patients with ConHD[3].

The incidence rate of sudden cardiac death in athletes is low and the total sample size of 711 ConHD patients in all exercise training studies combined lacks power to compare the incidence rates of athletes to ConHD patients. Although we cannot assess the incidence rate of sudden cardiac death in patients with ConHD, we know that the incidence is not as high as sometimes feared by parents, teachers and physical activity coaches.

Remodeling

Training in healthy people, both adult as well as young athletes, results in enhanced contractility and improved diastolic filling of the heart. These positive changes are due to improved myocardial relaxation, better compliance, decrease in filling pressures and increased contribution of atrial contraction. Subsequently during exercise stroke volume increases and cardiac output may increase significantly[4-6]. Those studies that have assessed the physiological global or regional remodeling of the athletes heart were performed after years of exercise training[5, 7-10].

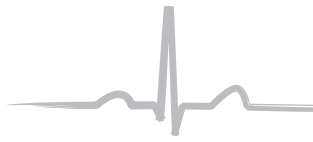
In contrast to the assessment of the athletes' heart after years of training, the effects of an exercise training program in patients with acquired heart disease have been assessed after a much shorter period, most often 12 weeks[9, 11-14]. In patients diagnosed with heart failure and reduced ejection fraction in the setting of acquired heart disease, positive cardiac outcomes have been reported after exercise training. These positive outcomes included: improvement of mitral inflow patterns; decrease of left ventricular dimension; increase in ejection fraction, decrease in mortality and hospitalization[9, 11-14]. Cardiac remodeling has not been a general finding in response to exercise training in patients with heart failure with preserved ejection fraction[15]. It is not yet clear whether the mechanism of heart failure, indicated by ejection fraction, accounts for the type of changes in cardiac outcomes.

The TOFFIT trial described in this thesis for the first time shows in a randomized control trial that exercise training in ConHD patients does not lead to adverse remodeling (**chapter 5 and 6**). The systolic as well as diastolic function remained unchanged. As diastolic dysfunction may precede systolic dysfunction, the lack of adverse changes in diastolic function is an important finding[16]. Previously 2 non-randomized ConHD exercise studies focused on cardiac changes. Only one study, using MRI to assess cardiac effects in 4 Fontan patients, noted an improvement of global ventricular performance after resistance training[17]. Another study, using echocardiography to assess the effect of an aerobic training program in 11 young ToF patients did not report any change[18].

The lack of remodeling, either positive or negative, seen in the TOFFIT trial may be due to several factors. Firstly no adverse remodeling may have occurred in these patients. The lack of positive remodeling might be due to the fact that the participants in our study were relatively too healthy to clearly measure the improvement in cardiac function, similar to patients with heart failure with preserved ejection fraction. Other factors, such as the duration or intensity of training, may account for the lack of clear improvement in cardiac function.

Wall shear stress in Fontan patients

Low dose dobutamine and physical stress MRI studies in Fontan patients have shown that end-diastolic volume decreases with stress[19, 20]. This may indicate diminished



ventricular performance or impaired preload in these patients[19]. Impaired preload may partly be due to pulmonary vascular dysfunction[21]. Pulmonary vascular dysfunction may be the result of increased pulmonary vascular resistance (PVR). In patients with a Fontan circulation PVR is thought to be a critical determinant of cardiac output[20]. The release of nitric oxide in the vessel results in vasodilation and subsequently decreases PVR. Shear stress at the vessel wall and pulsatility in the vessel regulate the release of nitric oxide by the endothelium[22]. Arterial remodeling has been associated with changes of wall shear stress (WSS) during exercise. In athletes vascular function improved due to arterial remodeling[24]. Hence if an exercise training program could enhance WSS in the pulmonary artery and if this might result in an increase of NO release in the pulmonary artery and thus in an enhanced ventricular preload reserve, this might ultimately result in an increase of cardiac output in Fontan patients. However, WSS did not increase after the exercise training program in our Fontan patients (**chapter 7**). Previous studies have shown that endothelial NO release was increased in patients with vascular dysfunction after exercise training, not in healthy people. It might be that pulmonary vascular dysfunction of our Fontan patients was not sufficiently impaired to show improvement with to be responsive to the type of training we prescribed[24]. In line with this hypothesis is the observation in a recent study that has shown that Fontan patients with a poorer baseline exercise capacity were able to enhance their exercise capacity more after the use of sildenafil, a NO pathway modifying drug, than those with higher baseline exercise capacity[25].SA relatively young and healthy cohort of Fontan patients who used sildenafil for 6 weeks failed to significantly improve their exercise capacity[26]. The lack of improvement in that study could be due to the relative healthy cohort. Whether our exercise training did not influence NO release by endothelium in Fontan patients, or as previously stated, we selected a relative healthy Fontan cohort in which the room to improve was limited remains unknown.

Neurohormonal assessment

Exercise training has been associated with favorable changes in the inflammatory balance in studies with acquired heart disease patients[27, 28].In heart failure patients a training program resulted in significant decrease of NT-pro BNP[29]. We did not see a decrease of NT pro-BNP levels in our patients (**chapter 5**). However, the baseline measurements in the heart failure studies were much higher than the NT-pro BNP measurements in our cohort. We measured NT pro-BNP levels within normal or slightly increased ranges. This may relate to differences in pathophysiology between acquired and congenital heart disease, or to differences in disease state at the time of the exercise training. Our patients were in relatively good clinical state, without signs of heart failure. This may explain the limited favorable effect that we noted.

IS A STANDARDIZED AEROBIC DYNAMIC EXERCISE TRAINING PROGRAM EFFECTIVE?

Important aspects of an exercise training program are the effects on physical fitness and on physical activity levels. We will discuss these effects of the used standardized exercise training program.

Daily physical activity

Public health guidelines suggest that children should be moderately to vigorously active for at least 60 minutes per day. Nowadays children with ConHD are advised to follow the general health guidelines[30]. Seventy percent of our patients were moderately to vigorously active for more than 60 minutes per day at baseline, which is much higher than described in other international studies involving ConHD patients (**chapter 4**)[31-33]. Physical activity may be related to geographic location and associated cultural differences. For instance, in the United States of America commuting to school is mostly done by car or bus, whereas in the Netherlands most children use a bicycle.

We concluded from our study that encouraging patients with ConHD to participate in an exercise training program does not increase their physical daily activity. In contrast, physical activity of adolescents with ConHD has been shown to increase in an exercise training program which included psychological intervention[34]. A multidisciplinary approach may be required to successfully change daily physical activity levels[35]. Physicians can contribute by encouraging their ConHD patients to be physical active. Swan et al. reported that only 19% of the adult ConHD patients had been encouraged to exercise by their physician. In 71% of the patients the topic of exercise had not been raised by their physician[36]. Patients should be encouraged at a young age. An inactive adolescent is less likely to be active as an adult[37].

Physical fitness

Physical performance increased after the exercise training program in ToF-patients, but not in Fontan-patients (**chapter 4**). In response to our training program, peakVO_2 increased in the ToF exercise-group, although this did not significantly differ from the control group. However, the significant increase in workload, ventilation and heart rate recovery in the ToF exercise-group compared to the control-group point in the direction of improved cardio-pulmonary fitness. The increase in peakVO_2 of 3 ml/kg/min (5%) in our ToF-patients is in the same range as the increase in peakVO_2 reported in a pilot study with adult ToF-patients as well as in other exercise studies among heterogeneous groups of ConHD patients and exercise studies in healthy adolescents (**chapter 2**) (5–6%)[38, 39]. We therefore think that the exercise training program has increased physical fitness in ToF patients.

In contrast to the ToF-patients, Fontan-patients did not increase their peakVO_2 after exercise training. The workload as well as ventilation and heart rate recovery did not increase either. The lack of increase in PeakVO_2 is in contrast with most previous exercise studies in adult Fontan-patients as well as in 3 out of 4 exercise studies in younger Fontan-patients[17, 40-43]. The most likely explanation for these contrasting findings may be related to the low baseline peakVO_2 of 25-28 ml/kg/min in previous studies compared to a baseline peakVO_2 of 33 ml/kg/min in our study[44]. A relatively high physical exercise capacity baseline may limit the room for improvement.

An additional explanation for the unchanged PeakVO_2 after the exercise training program may be the lack of increase in stroke volume in Fontan patients, as we demonstrated with (stimulated) cardiac stress, using low-dose dobutamine. This indicates that the increase in cardiac output relies on heart rate. Thus stroke volume will not increase as it would in healthy people when exercise demands it. The lack of increase in stroke volume most likely relates to preload impairment in the Fontan circulation as described in a paragraph above[19, 45]. This suggests that exercise capacity is intrinsically limited in Fontan patients. We speculate that Fontan-patients may reach a plateau in their capability to enhance stroke volume and thus cardiac output, which may reduce the potential increase in peakVO_2 with an exercise training program.

The standardized exercise training program

Strict supervision and monitoring of the training sessions and of training intensity assured that the required training effort was delivered. This is reflected in our below average drop out percentage (3%) in comparison to a mean of 16% in previous exercise studies in ConHD (**chapter 2**). Compared to previous studies, training adherence in our participants (89%) was also above the reported average of 80%. We consider the strict supervision and monitoring to be a strength of our study.

The large majority of the studies reported in literature on exercise in ConHD have used dynamic submaximal exercise. A small number the studies have used resistance training. Muscle strength is an important parameter for functional daily life activities and improvement will benefit the patient[46]. Strength (resistance) training has been used in patients with heart failure in acquired heart disease[9, 47, 48]. Since muscle wasting is commonly observed, improved function of skeletal muscle, including breathing musculature, will result in positive effects of exercise training[9, 47-49]. High intensity training schemes have also been used in acquired heart disease patients nowadays. The results of both resistance and high intensity training schemes in patients with an acquired heart disease have been equivocal[14]. Although strength training was not studied in ConHD often, it might be wise to reconsider the 'no strength training' dogma that is commonly applied in these patients[50]. We have not yet tested the different training types in large enough population with patients with ConHD to distinguish the most appropriate training program for this population.

CAN A STANDARDIZED AEROBIC DYNAMIC EXERCISE TRAINING PROGRAM IMPROVE THE QUALITY OF LIFE?

Children, especially those with a low baseline health related quality of life (HRQoL) improved on self-reported cognitive functioning after the training program (**chapter 8**). In contrast in adolescents and young adults the exercise training program did not change the quality of life (QoL). This may be due to the fact that most adolescents had best-possible scores at baseline. They also reported better QoL compared to peers. As the trial was optional for patients to join, a selection bias toward the more motivated patients may have occurred which may be reflected in the high baseline scores. This adds to the suggestion mentioned in one of the above paragraphs that we included a relatively healthy study population. The change in QoL has scarily been the subject of the exercise intervention studies so far[51]. Of the studies that have measured QoL, none has used a psychological intervention along the exercise training program. As mentioned above a multidisciplinary approach may successfully change daily physical activity levels. This might also change QoL after an exercise training program[34, 35]. The psychological intervention during the exercise training program should include the caregivers of the participants, since the psychological state of parents has an influence on the change of QoL after an exercise training program in their adolescents (**chapter 9**).

CLINICAL IMPLICATIONS

ToF and Fontan patients are among the ConHD patients with the highest risk to develop heart failure[52]. Therefore, they may be considered the patients to benefit the most from potential positive effects of exercise training as seen in healthy peers[53]. Reluctance of physicians to refer patients with ConHD to exercise programs has been suggested to be among the reasons for low participation in exercise programs of these patients[36, 54]. Most studies involving children and young adults with ConHD exercise, including the study in this thesis, have reported an increase in exercise capacity and have shown that the training program is safe, despite large variation in training schemes, the type of supervision of training and outcome measures. The evidence for the absence of adverse remodeling in these patients was lacking so far. We, for the first time, have reported the effect of an exercise training program on cardiac remodeling. The findings of our study put the perception of children and adolescents with ConHD as being "at risk" during physical activity in another perspective[2]. This may be reassuring for patients, parents and caretakers, and may help them to encourage children and young adults with ConHD to engage in physical activities. If patients are physical active at school-age they are most likely to be physically active as an adult[37].

The results of our study may contribute to improve quality of current recommendations for physical activity and exercise training in patients with ConHD and endorse that physical exercise training becomes part of the ConHD treatment[30, 55, 56].

STRENGTHS AND LIMITATIONS

The study described in this thesis finds strength in the fact that it is a randomized controlled trial. Further strength lays in the fact that all training sessions were supervised by a certified physiotherapist and every participant was given a heart rate monitor to ensure that exercise training sessions were performed within the desired heart rate range. This created an intervention period, in which it was ensured that the exercise training was well executed. The success of the study design was reflected in the 89% adherence to training sessions.

Exercise training studies in patients with acquired heart diseases have included up to 2311 patients. Our study included 93 patients, which is 15% of all ConHD patients participating in exercise training programs that have been reported on in literature ever[57]. Our number of patients is the largest in exercise training studies performed in ConHD patients. The participation rate of 26% of the total eligible patients is in line with other exercise training studies[40, 58]. Most patients that did not participate judged the study to be too intense and time-consuming. The study consisted of two full-day hospital visits and a possibility to have to engage in exercise training 3 times per week for 12 weeks. The low-dropout rate of 3 patients (3%) indicates that the structured and supervised study was well executed.

Due to the intensity of the training we may have created an inclusion bias, as only the patients motivated to participate in exercise training sessions were enrolled. This may have resulted in a relative high exercise capacity at baseline, which may have restricted the room for improvement. In contrast to our design, other exercise training studies in ConHD patients have used an exclusion criteria of peakVO_2 > 80%[43, 51, 59]. In retrospect, if we had used that exclusion criterion, we might have included a less physical fit group of ConHD patients. This might have resulted in different findings. On the other hand, this would have diminished the number of participants, and therefore decrease the power of the study.

Since this was a multi-center trial we had to use different set-ups for exercise testing in our study. However, we do not think that this has affected our main outcome measures, since all centers used the same protocol, had state of the art equipment and, moreover, patients served as their own controls. We have assessed our follow-up measurements within 2 weeks of the intervention period. We have not assessed long-term follow-up, potentially missing adverse or positive cardiac remodeling.

FUTURE RESEARCH

The aim of this thesis was to investigate if a standardized aerobic dynamic exercise training program is safe, effective and quality of life improving in children and young adults with corrected tetralogy of Fallot and Fontan circulation.

On the basis of our results several questions remain. These include:

1) How to improve physical activity levels in congenital heart disease?

Our study has shown that exercise training alone does not increase physical activity in patients with ConHD. Other interventions, such as psychosocial, or combinations of interventions are required to achieve sustained changes in behavior that will increase physical activity levels in these patients. This may be of importance for prevention of general health problems, including cardiovascular disease, in these patients. Based on our results we suggest studying the effects of multidisciplinary and multimodal approaches.

2) Which type of exercise training program is most effective to improve fitness in patients with congenital heart disease?

Studies in patients with heart failure due to acquired heart disease have utilized different types of exercise training, such as high intensity / anaerobic exercise training, strength / resistance training and aerobic exercise programs. Our results indicate that dynamic aerobic exercise training may not be the single best option for all types of ConHD. Based on our results we suggest studying the effects of different types of exercise training in patients with different types of ConHD. In addition to assessing the different types we also recommend establishing a core-set of outcome measures to improve the benchmarking of different training protocols.

3) What are the long-term effects of an exercise training program in patients with congenital heart disease?

Information on long-term sustainability of training programs is scarce. The results of the available studies provide evidence for a long-term sustainability of improved exercise capacity, measured up to 10 months after the exercise program[43, 51, 60]. Although these results are encouraging, the sample size is small and follow-up duration is short. Further studies are required to assess the long-term effects of exercise training programs in congenital heart disease and the effects of different type of exercise training in these patients.

4) Which mechanisms apply to the cardiac remodeling related to exercise training in congenital heart disease?

In acquired heart disease, beneficial effects of exercise training have been shown with regard to cardiac hypertrophy, the contraction and relaxation machinery, angiogenesis, inflammatory balance and renewal and regeneration capability. These effects have hardly been studied in ConHD. It may be hypothesized that some of these mechanisms may be used to add to the prevention of heart failure related to ConHD. Clearly, further studies are needed to study the basic mechanisms of cardiovascular changes in relation to exercise training in (models of) congenital heart disease.

Our training program, with good adherence, did not lead to alterations in cardiac remodeling. Systolic and diastolic function, both global as well as regional, heart rate and arrhythmia, wall shear stress, distensibility and pulsatility did not change. To assess long-term effects a second follow-up assessment would have been needed. We unfortunately were unable to include such a subsequent follow-up visit in our trial. We have chosen to perform an exercise study with an aerobic training design. We did not investigate the effects of resistance training or a high intensity exercise program. In addition further research is warranted to establish if this young cohort will remain free of morbidity as well as the effect of an exercise training program on future morbidity.

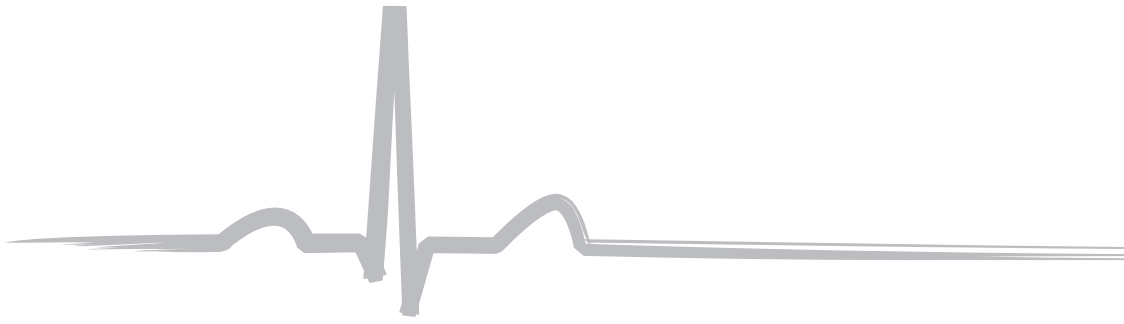
REFERENCES

1. Schmied C, Borjesson M. Sudden cardiac death in athletes. *J Intern Med*. 2014;275:93-103
2. Moola F, Fusco C, Kirsh JA. The perceptions of caregivers toward physical activity and health in youth with congenital heart disease. *Qual Health Res*. 2011;21:278-291
3. Zipes DP, Ackerman MJ, Estes NA, 3rd, Grant AO, Myerburg RJ, Van Hare G. Task force 7: Arrhythmias. *J Am Coll Cardiol*. 2005;45:1354-1363
4. Pela G, Bruschi G, Montagna L, Manara M, Manca C. Left and right ventricular adaptation assessed by doppler tissue echocardiography in athletes. *J Am Soc Echocardiogr*. 2004;17:205-211
5. La Gerche A, Taylor AJ, Prior DL. Athlete's heart: The potential for multimodality imaging to address the critical remaining questions. *JACC Cardiovasc Imaging*. 2009;2:350-363
6. Baggish AL, Wood MJ. Athlete's heart and cardiovascular care of the athlete: Scientific and clinical update. *Circulation*. 2011;123:2723-2735
7. Zdravkovic M, Perunicic J, Krotin M, Ristic M, Vukomanovic V, Soldatovic I, Zdravkovic D. Echocardiographic study of early left ventricular remodeling in highly trained preadolescent footballers. *J Sci Med Sport*. 2010;13:602-606
8. Sharma S, Maron BJ, Whyte G, Firoozi S, Elliott PM, McKenna WJ. Physiologic limits of left ventricular hypertrophy in elite junior athletes: Relevance to differential diagnosis of athlete's heart and hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2002;40:1431-1436
9. Alves AJ, Ribeiro F, Goldhammer E, Rivlin Y, Rosenschein U, Viana JL, Duarte JA, Sagiv M, Oliveira J. Exercise training improves diastolic function in heart failure patients. *Med Sci Sports Exerc*. 2012; 44:776-785
10. Nottin S, Doucende G, Schuster-Beck I, Dauzat M, Obert P. Alteration in left ventricular normal and shear strains evaluated by 2d-strain echocardiography in the athlete's heart. *The Journal of physiology*. 2008;586:4721-4733
11. Erbs S, Hollriegel R, Linke A, Beck EB, Adams V, Gielen S, Mobius-Winkler S, Sandri M, Krankel N, Hambrecht R, Schuler G. Exercise training in patients with advanced chronic heart failure (nyha iiib) promotes restoration of peripheral vasomotor function, induction of endogenous regeneration, and improvement of left ventricular function. *Circ Heart Fail*. 2010;3:486-494
12. Piepoli MF, Davos C, Francis DP, Coats AJ, ExTra MC. Exercise training meta-analysis of trials in patients with chronic heart failure (extramatch). *BMJ*. 2004;328:189
13. Swift DL, Lavie CJ, Johannsen NM, Arena R, Earnest CP, O'Keefe JH, Milani RV, Blair SN, Church TS. Physical activity, cardiorespiratory fitness, and exercise training in primary and secondary coronary prevention. *Circ J*. 2013;77:281-292
14. Haykowsky MJ, Liang Y, Pechter D, Jones LW, McAlister FA, Clark AM. A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: The benefit depends on the type of training performed. *J Am Coll Cardiol*. 2007;49:2329-2336
15. Taylor RS, Davies EJ, Dalal HM, Davis R, Doherty P, Cooper C, Holland DJ, Jolly K, Smart NA. Effects of exercise training for heart failure with preserved ejection fraction: A systematic review and meta-analysis of comparative studies. *Int J Cardiol*. 2012;162:6-13
16. van den Berg J, Wielopolski PA, Meijboom FJ, Witsenburg M, Bogers AJ, Pattynama PM, Helbing WA. Diastolic function in repaired tetralogy of fallot at rest and during stress: Assessment with mr imaging. *Radiology*. 2007;243:212-219
17. Cordina RL, O'Meagher S, Karmali A, Rae CL, Liess C, Kemp GJ, Puranik R, Singh N, Celermajer DS. Resistance training improves cardiac output, exercise capacity and tolerance to positive airway pressure in fontan physiology. *Int J Cardiol*. 2013;168:780-788

18. Sklansky MS, Pivarnik JM, O'Brian Smith E, Morris J, Bricker JT. Exercise training hemodynamics and the prevalence of arrhythmia's in children following tetralogy of fallot repair. *Pediatric Exercise Science*. 1994;6:188-200
19. Robbers-Visser D, Jan Ten Harkel D, Kapusta L, Strengers JL, Dalinghaus M, Meijboom FJ, Pattynama PM, Bogers AJ, Helbing WA. Usefulness of cardiac magnetic resonance imaging combined with low-dose dobutamine stress to detect an abnormal ventricular stress response in children and young adults after fontan operation at young age. *Am J Cardiol*. 2008;101:1657-1662
20. Van De Bruaene A, La Gerche A, Claessen G, De Meester P, Devroe S, Gillijns H, Bogaert J, Claus P, Heidbuchel H, Gewillig M, Budts W. Sildenafil improves exercise hemodynamics in fontan patients. *Circ Cardiovasc Imaging*. 2014;7:265-273
21. Robbers-Visser D, Helderman F, Strengers JL, van Osch-Gevers L, Kapusta L, Pattynama PM, Bogers AJ, Krams R, Helbing WA. Pulmonary artery size and function after fontan operation at a young age. *J Magn Reson Imaging*. 2008;28:1101-1107
22. Green DJ, Spence A, Rowley N, Thijssen DH, Naylor LH. Vascular adaptation in athletes: Is there an 'athlete's artery'? *Experimental physiology*. 2012;97:295-304
23. Gewillig M, Brown SC, Eyskens B, Heying R, Ganame J, Budts W, La Gerche A, Gorenflo M. The fontan circulation: Who controls cardiac output? *Interact Cardiovasc Thorac Surg*. 2010;10:428-433
24. Green DJ. Exercise training as vascular medicine: Direct impacts on the vasculature in humans. *Exerc Sport Sci Rev*. 2009;37:196-202
25. Hager A, Weber R, Muller J, Hess J. Predictors of sildenafil effects on exercise capacity in adolescents and adults with fontan circulation. *Clin Res Cardiol*. 2014;3:1-6
26. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, Hanna BD, Wernovsky G, Paridon SM, Rychik J. Impact of oral sildenafil on exercise performance in children and young adults after the fontan operation: A randomized, double-blind, placebo-controlled, crossover trial. *Circulation*. 2011;123:1185-1193
27. Ploeger HE, Takken T, de Greef MH, Timmons BW. The effects of acute and chronic exercise on inflammatory markers in children and adults with a chronic inflammatory disease: A systematic review. *Exerc Immunol Rev*. 2009;15:6-41
28. Lavie CJ, Church TS, Milani RV, Earnest CP. Impact of physical activity, cardiorespiratory fitness, and exercise training on markers of inflammation. *J Cardiopulm Rehabil Prev*. 2011;31:137-145
29. Passino C, Severino S, Poletti R, Piepoli MF, Mammini C, Clerico A, Gabutti A, Nassi G, Emdin M. Aerobic training decreases b-type natriuretic peptide expression and adrenergic activation in patients with heart failure. *J Am Coll Cardiol*. 2006;47:1835-1839
30. Takken T, Giardini A, Reybrouck T, Gewillig M, Hovels-Gurich HH, Longmuir PE, McCrindle BW, Paridon SM, Hager A. Recommendations for physical activity, recreation sport, and exercise training in paediatric patients with congenital heart disease: A report from the exercise, basic & translational research section of the european association of cardiovascular prevention and rehabilitation, the european congenital heart and lung exercise group, and the association for european paediatric cardiology. *Eur J Prev Cardiol*. 2012;19:1034-1065
31. Arvidsson D, Slinde F, Hulthen L, Sunnegardh J. Physical activity, sports participation and aerobic fitness in children who have undergone surgery for congenital heart defects. *Acta Paediatr*. 2009; 98:1475-1482
32. Massin MM, Hovels-Gurich HH, Gerard P, Seghaye MC. Physical activity patterns of children after neonatal arterial switch operation. *Ann Thorac Surg*. 2006;81:665-670

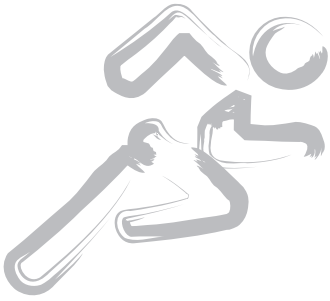
33. McCrindle BW, Williams RV, Mital S, Clark BJ, Russell JL, Klein G, Eisenmann JC. Physical activity levels in children and adolescents are reduced after the fontan procedure, independent of exercise capacity, and are associated with lower perceived general health. *Arch Dis Child*. 2007;92:509-514
34. Morrison ML, Sands AJ, McCusker CG, McKeown PP, McMahon M, Gordon J, Grant B, Craig BG, Casey FA. Exercise training improves activity in adolescents afflicted with congenital heart disease. *Heart*. 2013;99(15):1122-1128
35. Giannakoulas G, Dimopoulos K. Exercise training in congenital heart disease: Should we follow the heart failure paradigm? *Int J Cardiol*. 2010;138:109-111
36. Swan L, Hillis WS. Exercise prescription in adults with congenital heart disease: A long way to go. *Heart*. 2000;83:685-687
37. Telama R, Yang X, Viikari J, Valimaki I, Wanne O, Raitakari O. Physical activity from childhood to adulthood: A 21-year tracking study. *Am J Prev Med*. 2005;28:267-273
38. Therrien J, Fredriksen P, Walker M, Granton J, Reid GJ, Webb G. A pilot study of exercise training in adult patients with repaired tetralogy of fallot. *Can J Cardiol*. 2003;19:685-689
39. Baquet G, van Praagh E, Berthoin S. Endurance training and aerobic fitness in young people. *Sports Med*. 2003;33:1127-1143
40. Winter MM, van der Bom T, de Vries LC, Balducci A, Bouma BJ, Pieper PG, van Dijk AP, van der Plas MN, Picchio FM, Mulder BJ. Exercise training improves exercise capacity in adult patients with a systemic right ventricle: A randomized clinical trial. *Eur Heart J*. 2012;33:1378-1385
41. Minamisawa S, Nakazawa M, Momma K, Imai Y, Satomi G. Effect of aerobic training on exercise performance in patients after the fontan operation. *Am J Cardiol*. 2001;88:695-698
42. Opocher F, Varnier M, Sanders SP, Tosoni A, Zaccaria M, Stellin G, Milanesi O. Effects of aerobic exercise training in children after the fontan operation. *Am J Cardiol*. 2005;95:150-152
43. Singh TP, Curran TJ, Rhodes J. Cardiac rehabilitation improves heart rate recovery following peak exercise in children with repaired congenital heart disease. *Pediatr Cardiol*. 2007;28:276-279
44. Robbers-Visser D, Kapusta L, van Osch-Gevers L, Strengers JL, Boersma E, de Rijke YB, Boomsma F, Bogers AJ, Helbing WA. Clinical outcome 5 to 18 years after the fontan operation performed on children younger than 5 years. *J Thorac Cardiovasc Surg*. 2009;138:89-95
45. Hager A, Fratz S, Schwaiger M, Lange R, Hess J, Stern H. Pulmonary blood flow patterns in patients with fontan circulation. *Ann Thorac Surg*. 2008;85:186-191
46. Nettle H, Sprogis E. Pediatric exercise: Truth and/or consequences. *Sports Med Arthrosc*. 2011;19: 75-80
47. Spruit MA, Eterman RM, Hellwig VA, Janssen PP, Wouters EF, Uszko-Lencer NH. Effects of moderate-to-high intensity resistance training in patients with chronic heart failure. *Heart*. 2009;95: 1399-1408
48. Cantinotti M, Lopez L. Nomograms for blood flow and tissue doppler velocities to evaluate diastolic function in children: A critical review. *J Am Soc Echocardiogr*. 2013;26:126-141
49. Conraads VM, Van Craenenbroeck EM, De Maeyer C, Van Berendoncks AM, Beckers PJ, Vrints CJ. Unraveling new mechanisms of exercise intolerance in chronic heart failure: Role of exercise training. *Heart Fail Rev*. 2013;18:65-77
50. Tikkanen AU, Oyaga AR, Riano OA, Alvaro EM, Rhodes J. Paediatric cardiac rehabilitation in congenital heart disease: A systematic review. *Cardiol Young*. 2012:1-10
51. Rhodes J, Curran TJ, Camil L, Rabideau N, Fulton DR, Gauthier NS, Gauvreau K, Jenkins KJ. Sustained effects of cardiac rehabilitation in children with serious congenital heart disease. *Pediatrics*. 2006; 118:e586-593

52. Norozi K, Wessel A, Alpers V, Arnhold JO, Geyer S, Zoege M, Buchhorn R. Incidence and risk distribution of heart failure in adolescents and adults with congenital heart disease after cardiac surgery. *Am J Cardiol*. 2006;97:1238-1243
53. Ortega FB, Ruiz JR, Castillo MJ, Sjostrom M. Physical fitness in childhood and adolescence: A powerful marker of health. *Int J Obes (Lond)*. 2008;32:1-11
54. Grace SL, Gravely-Witte S, Brual J, Monette G, Suskin N, Higginson L, Alter DA, Stewart DE. Contribution of patient and physician factors to cardiac rehabilitation enrollment: A prospective multilevel study. *Eur J Cardiovasc Prev Rehabil*. 2008;15:548-556
55. Hirth A, Reybrouck T, Bjarnason-Wehrens B, Lawrenz W, Hoffmann A. Recommendations for participation in competitive and leisure sports in patients with congenital heart disease: A consensus document. *Eur J Cardiovasc Prev Rehabil*. 2006;13:293-299
56. Budts W, Borjesson M, Chessa M, van Buuren F, Trigo Trindade P, Corrado D, Heidbuchel H, Webb G, Holm J, Papadakis M. Physical activity in adolescents and adults with congenital heart defects: Individualized exercise prescription. *Eur Heart J*. 2013;34:3669-3674
57. Mentz RJ, Schulte PJ, Fleg JL, Fiuzat M, Kraus WE, Pina IL, Keteyian SJ, Kitzman DW, Whellan DJ, Ellis SJ, O'Connor CM. Clinical characteristics, response to exercise training, and outcomes in patients with heart failure and chronic obstructive pulmonary disease: Findings from heart failure and a controlled trial investigating outcomes of exercise training (hf-action). *Am Heart J*. 2013;165: 193-199
58. Dua JS, Cooper AR, Fox KR, Graham Stuart A. Exercise training in adults with congenital heart disease: Feasibility and benefits. *Int J Cardiol*. 2010;138:196-205
59. Rhodes J, Curran TJ, Camil L, Rabideau N, Fulton DR, Gauthier NS, Gauvreau K, Jenkins KJ. Impact of cardiac rehabilitation on the exercise function of children with serious congenital heart disease. *Pediatrics*. 2005;116:1339-1345
60. Longmuir PE, Tremblay MS, Goode RC. Postoperative exercise training develops normal levels of physical activity in a group of children following cardiac surgery. *Pediatr Cardiol*. 1990;11:126-130



Chapter 11

Summary



In **chapter 1** we elaborated on the prevalence of congenital heart disease (ConHD). We described the patient population with corrected tetralogy of Fallot (ToF) and the patient population with a univentricular heart who were given a Fontan circulation. We gave an overview of the randomized controlled trial used in part 2.

In **chapter2** we discussed the known literature on the subject of exercise intervention training in patients with ConHD. Although the design of the 29 included studies differed, most studies concluded that exercise training improves exercise capacity in patients with ConHD. A minority of the studies mentioned adverse events, and none of the studies elaborated on the effect of an exercise training on cardiac remodeling.

In **chapter 3** we investigated the long-term outcomes in patients with tetralogy of Fallot (ToF). ToF patients corrected with the transatrial–transpulmonary approach have good long-term survival. Over several decades, the operative mortality (5 of 453 patients) was 1.1%, and 25-year overall survival rate was 92%, more specifically 91% in the transannular patch (TP) group and 96% in the non-TP group. Pulmonary valve replacement was a frequent event at longer follow-up and other events are limited. The use of a TP is a predictor for poorer event-free outcomes.

In **chapter 4** we showed that patients with corrected tetralogy of Fallot (ToF) improved their exercise capacity after an 12 week aerobic exercise training program. Patients with a Fontan circulation (Fontan patients) did not improve their exercise capacity. The Fontan patients were relatively fit before the start of the trial. We speculated that they were unable to increase cardiac output and thus exercise capacity. Daily physical activity did not increase after the training program.

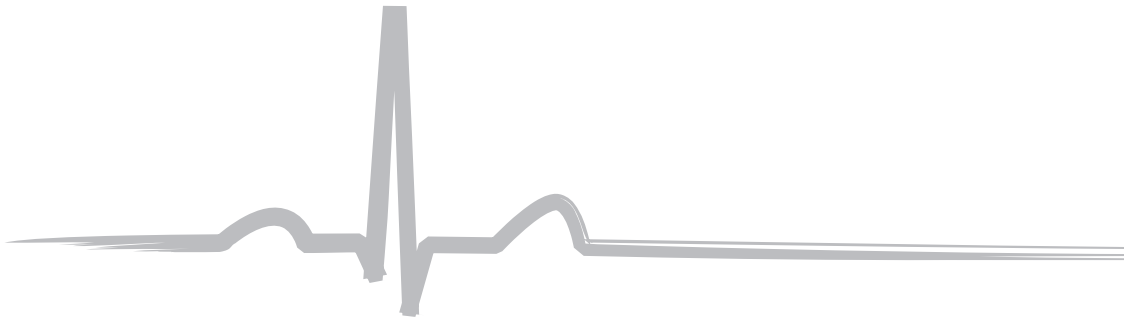
In **chapter 5 and chapter 6** we showed that a 12 week aerobic exercise training program did not result in adverse cardiac remodeling. Systolic and diastolic global cardiac function remained unchanged after the training program in ToF and Fontan patients. In line with the findings on global cardiac function, regional ventricular functioning did not change either.

In **chapter 7** we assessed the wall shear stress (WSS) in the pulmonary artery in Fontan patients. WSS contributes to the release of NO in the vessel, allowing vasodilatation. WSS in the pulmonary artery was lower in Fontan patients that in healthy peers. A 12 week exercise training program did not change WSS levels in Fontan patients.

In **chapter 8** we showed that an exercise program improved self-reported cognitive functioning in children between 10 and 15 years. In contrast, the exercise program did not improve the quality of life (QoL) of patients aged 16-25 years. This might be explained by their high self-reported baseline QoL. Another explanation is that a more age-appropriate sports-intervention, with more focus on obtaining autonomy and belonging to a peer-group, involving more 'normal' sports-participation with healthy peers, might have given better results.

In **chapter 9** we showed that parental mental health was a significant moderator for effects of exercise training on HRQoL in their children. Parental anxiety and overprotection may hamper participation of children with ConHD in physical activities. Adolescents in the exercise group reported a pre-post decrease in social functioning when their parents themselves reported more mental health problems and more specifically: more parental anxiety/insomnia and severe depression.

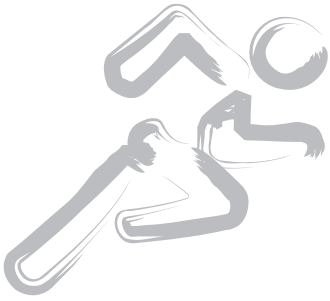
In **chapter 10** we discussed the findings of the previous chapters. We concluded that a 12 week aerobic exercise training program is safe. The training program improved exercise capacity in tetralogy of Fallot patients, but not in relatively healthy Fontan patients. Cardiac function remained unchanged after the training program in ToF and Fontan patients. Health related quality of life improved after a training program, especially if baseline quality of life was low. We elaborated on the strength and limitations of the study. Based on our result we suggested ideas for future research.



Chapter 12

Dutch summary

Nederlandse samenvatting



In **hoofdstuk 1** hebben we de prevalentie van aangeboren hartafwijkingen besproken, waarbij we uitgebreid hebben stil gestaan bij de aandoeningen tetralogie van Fallot en het univentriculaire hart. Tevens hebben we in hoofdstuk 1 een uiteenzetting gegeven van het multi-centrum gerandomiseerde gecontroleerde experiment waarop de resultaten van hoofdstuk 4 tot 9 gestoeld zijn.

In **hoofdstuk 2** hebben we de bekende literatuur over het effect van trainingsprogramma's bij patiënten met een aangeboren hartafwijking bediscussieerd. De 29 geïncludeerde studies verschillen in opzet. De meeste studies concludeerden dat de training het uithoudingsvermogen van patiënten met een aangeboren hartafwijking verbeterde. Een minderheid van de studies rapporteerde over het voorkomen van schadelijke incidenten. Geen van de studies onderzocht het effect van de training op cardiale veranderingen in de patiënten.

In **hoofdstuk 3** hebben we de lange termijn uitkomsten van patiënten met een tetralogie van Fallot beschreven. Patiënten met een transatriale-transpulmonaire operatie hebben een goede lange termijn overleving. De mortaliteit tijdens de operatie was 1,1%, en de overleving van na 25 jaar was 92%. Uitgesplitst naar operatie techniek was de overleving 91% voor diegene waarbij een transannulair stuk gebruikt werd en 96% voor diegene waarbij geen transannulair stuk gebruikt werd.

In **hoofdstuk 4** hebben we laten zien dat patiënten met een tetralogie van Fallot hun uithoudingsvermogen hebben verbeterd na een twaalf weeks trainingsprogramma. Patiënten met een Fontan circulatie verbeterden hun uithoudingsvermogen na hetzelfde trainingsprogramma niet. De patiënten met een Fontan circulatie die participeerden in het onderzoek waren relatief fit voor de start van het onderzoek. We speculeerden dat ze hun hartminuutvolume niet hebben kunnen verbeteren waardoor hun uithoudingsvermogen niet verbeterde. De patiënten in het onderzoek hebben hun dagelijkse fysieke activiteit niet verhoogd na het trainingsprogramma.

In **hoofdstuk 5 en 6** hebben we laten zien dat het trainingsprogramma niet resulteerde in negatieve cardiale veranderingen. Zowel systolische als diastolische globale cardiale functies bleven onveranderd na het trainingsprogramma in zowel patiënten met een tetralogie van Fallot als patiënten met een Fontan circulatie. Ook de regionale cardiale functie veranderde niet na een trainingsprogramma.

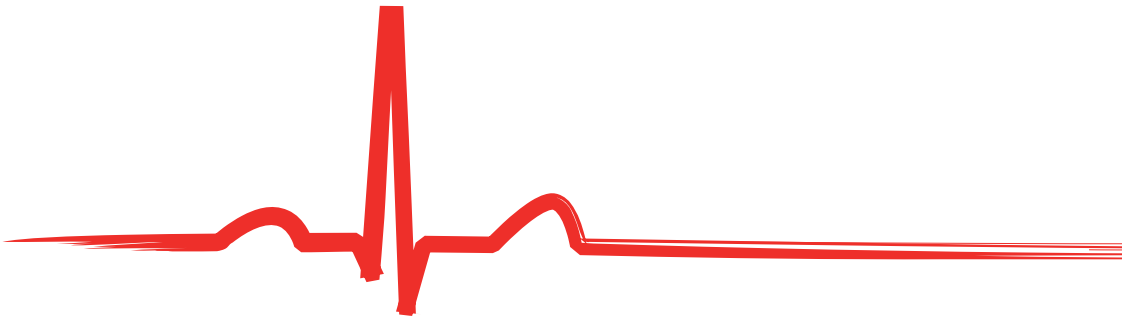
In **hoofdstuk 7** hebben we de schuifspanning van de pulmonale arterie in Fontan patiënten bestudeerd. De schuifspanning draagt bij aan het vrijkomen van stikstofmonoxide (NO) in de arterie, wat zorgt voor vaatverwijding. De schuifspanning in de pulmonale arterie is lager in patiënten met een Fontan circulatie ten opzichte van gezonde leeftijdsgenoten. Het trainingsprogramma veranderde de schuifspanning niet in patiënten met een Fontan circulatie.

In **hoofdstuk 8** hebben we laten zien dat het trainingsprogramma het zelf gerapporteerde cognitieve functioneren verbeterde in de groep patiënten tussen 10 en 15 jaar

oud. In contrast hiermee verbeterde de kwaliteit van leven niet van patiënten tussen de 16 en 25 jaar. Een mogelijke verklaring hiervoor is de hoge zelf gerapporteerde kwaliteit van leven voor aanvang van het trainingsprogramma. Een andere verklaring kan zijn dat het gekozen trainingsprogramma niet optimaal was. Mogelijk had een meer leeftijd geschikte sport interventie, met de focus meer op het verkrijgen van autonomie en het kunnen participeren met gezonde leeftijdsgenoten, wel effect had gehad op kwaliteit van leven.

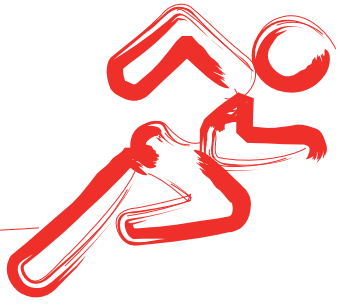
In **hoofdstuk 9** hebben we laten zien dat de ouderlijke mentale gezondheid een moderator is op het effect van een trainingsprogramma op kwaliteit van leven bij hun kinderen. Ouderlijke angsten en overbescherming kunnen een negatieve invloed hebben op de participatie aan fysieke activiteiten van hun kind met aangeboren hartafwijking. Adolescenten met ouders welke zelf angst en slapeloosheid rapporteerden scoorden hun sociaal functioneren na het trainingsprogramma lager.

In **hoofdstuk 10** bediscussiërden we onze bevindingen in de bovengenoemde hoofdstukken. We hebben geconcludeerd dat een 12 weeks trainingsprogramma veilig is. Het trainingsprogramma verbeterde het uithoudingsvermogen in patiënten met een tetralogie van Fallot, maar niet in de al relatief fitte patiënten met een Fontan circulatie. De cardiale functie bleef onveranderd na een trainingsprogramma in zowel tetralogie van Fallot patiënten als patiënten met een Fontan circulatie. Kwaliteit van leven verbeterde na een trainingsprogramma. Met name als de kwaliteit van leven voor het trainingsprogramma laag was. We benoemden de sterke en minder sterke punten van de studie. Als laatste suggereerden we ideeën na aanleiding van onze bevindingen voor toekomstig onderzoek.



Part 4

Appendices



List of abbreviations

A'	peak late diastolic myocardial velocity
ANOVA	analysis of variance
AP4CH	apical four-chamber view
APSE	annular plane systolic excursion
APVS	absent pulmonary valve syndrome
AVSD	atrioventricular septal defect
BSA	body mass area
CF	child form
CFD	computational fluid dynamics
CI	confidence interval
ConHD	congenital heart disease
CONHD-TAAQOL	congenital heart disease-TNO/AZL Adult Quality of Life
CONSORT	consolidated standards of reporting trials
CPAP	continuous positive airway pressure
CPET	cardiopulmonary exercise test
D	peak diastolic flow
DORV	double outlet right ventricle
E'	peak early diastolic myocardial velocity
ECC	extracardiac conduit
EDV	end-diastolic volume
EF	ejection fraction
EMC	Erasmus Medical Center
ESV	end-systolic volume
GBA	municipal basic administration
GHQ-28	general health questionnaire-28
HR	heart rate
HRQoL	health related quality of life
ICD	internal cardioverter-defibrillator
ILT	intracardial lateral tunnel
IQR	inter quartile range
IVS	interventricular septum
IVSd	interventricular septum thickness in diastole
IVSs	interventricular septum thickness in systole
LAS	linear analogue scale

LPA	left pulmonary artery
LVPWd	left ventricular posterior wall dimension in diastole
MAPSE	mitral annular plane systolic excursions
MET	metabolic equivalent
MR	magnetic resonance
MRI	magnetic resonance imaging
NT-pro-BNP	N-terminal pro-brain natriuretic peptide
OUES	oxygen uptake efficiency slope
PA	pulmonary artery
PA	pulmonary atresia
PAH	pulmonary hypertension
PC	phase-contrast
peakHR	peak heart rate
peakO_2Pulse	peak oxygen pulse
peakVE	peak minute ventilation
peakVO_2	peak oxygen uptake
PF	parent form
PR	pulmonary regurgitation
PS	pulmonary stenosis
PVR	pulmonary valve replacement
RER	respiratory exchange ratio
RPA	right pulmonary artery
RUMC	Radboud University Medical Center Nijmegen
RUPV	right upper pulmonary vein
RVIDd	right ventricle internal diameter in diastole
RVIDs	right ventricle internal diameter in systole
RVOT	right ventricular outflow tract
S	peak systolic flow
S'	peak systolic myocardial velocity
SD	standard deviation
SF-36	SF-36 Health Survey
SSE	Family support for Exercise Habits Scale: Participation and Involvement
SSFP	steady-state free precession
SV	stroke volume
SVC	superior vena cava
SV_i	indexed stroke volume
TACQOL	TNO/AZL Child Quality of Life Questionnaire
TACQOL-CF	TNO/AZL Child Quality of Life Questionnaire Child Form

TAPSE	tricuspid annular plane systolic excursions
TCPC	total cavopulmonary connection
TDI	tissue Doppler imaging
TGA	transposition of the great arteries
ToF	tetralogy of Fallot
TP	transannular patch
TR	tricuspid regurgitation
VACTERL	vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula and/or esophageal atresia, renal & radial anomalies and limb defects
$VATVO_2$	ventilatory anaerobic threshold VO_2
VCO_2	carbon dioxide outflow
VE	minute ventilation
VE/VCO_2-slope	minute ventilation to carbon dioxide production slope
VO_2	oxygen uptake
VSD	ventricular septal defect
WSS	wall shear stress

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List of publications

Does exercise training improve cardio-pulmonary fitness and daily physical activity in children and young adults with corrected tetralogy of Fallot or Fontan circulation? A randomized controlled trial.
Duppen N, Etnel JRG, Spaans L, Takken T, van den Berg-Emons RJ, Boersma E, Schokking M, Dulfer K, Utens EMWJ, Helbing WA, Hopman MTE
Am Heart J. 2015 jun. [Epub ahead of print].

Does functional health status predict health-related quality of life in children after Fontan operation?
Dulfer K, Bossers SS, Utens EM, **Duppen N**, Kuipers IM, Kapusta L, van Iperen G, Schokking M, Ten Harkel AD, Takken T, Helbing WA.
Cardiol Young. 2015 Apr 23:1-10. [Epub ahead of print]

Regional ventricular performance and exercise training in children and young adults after repair of tetralogy of Fallot: A randomized controlled pilot study.
Duppen N, Geerdink LM, Kuipers IM, Bossers SSM, Koopman L, van Dijk APJ, Roos-Hesselink JW, De Korte CL, Helbing WA, Kapusta L.
Circ Cardiovasc Imaging. 2015 Apr;8(4).

Long-term outcomes of transatrial-transpulmonary repair of tetralogy of Fallot.
Luijten LW, van den Bosch E, **Duppen N**, Tanke R, Roos-Hesselink J, Nijveld A, van Dijk A, Bogers AJ, van Domburg R, Helbing WA.
Eur J Cardiothorac Surg. 2015 Mar;47(3):527-34.

Parental mental health moderates the efficacy of exercise training on health-related quality of life in adolescents with congenital heart disease.
Dulfer K, **Duppen N**, Van Dijk AP, Kuipers IM, Van Domburg RT, Verhulst FC, Van der Ende J, Helbing WA, Utens EM.
Pediatr Cardiol. 2015 Jan;36(1):33-40.

The effect of exercise training on cardiac remodelling in children and young adults with corrected tetralogy of Fallot or Fontan circulation: a randomized controlled trial.
Duppen N, Kapusta L, de Rijke YB, Snoeren M, Kuipers IM, Koopman LP, Blank AC, Blom NA, Dulfer K, Utens EM, Hopman MT, Helbing WA.

Int J Cardiol. 2015 Jan 20;179:97-104.

Comprehensive rhythm evaluation in a large contemporary Fontan population.
Bossers SS, **Duppen N**, Kapusta L, Maan AC, Duim AR, Bogers AJ, Hazekamp MG, van Iperen G, Helbing WA, Blom NA.
Eur J Cardiothorac Surg. 2015 Jan 18; 548.

Exercise capacity in children after total cavopulmonary connection: lateral tunnel versus extracardiac conduit technique.
Bossers SS, Helbing WA, **Duppen N**, Kuipers IM, Schokking M, Hazekamp MG, Bogers AJ, Ten Harkel AD, Takken T.
J Thorac Cardiovasc Surg. 2014 Oct;148(4):1490-7.

Associations between exercise capacity, physical activity, and psychosocial functioning in children with congenital heart disease: a systematic review.
Dulfer K, Helbing WA, **Duppen N**, Utens EM.
Eur J Prev Cardiol. 2014 Oct;21(10):1200-15.

Effect of exercise training on sports enjoyment and leisure-time spending in adolescents with complex congenital heart disease: the moderating effect of health behavior and disease knowledge.
Dulfer K, **Duppen N**, Blom NA, van Dijk AP, Helbing WA, Verhulst FC, Utens EM.
Congenit Heart Dis. 2014 Sep-Oct;9(5):415-23.

Aerobic exercise influences quality of life of children and youngsters with congenital heart disease: a randomized controlled trial.
Dulfer K, **Duppen N**, Kuipers IM, Schokking M, van Domburg RT, Verhulst FC, Helbing WA, Utens EM.
J Adolesc Health. 2014 Jul;55(1):65-72.

Effects of exercise training on behavioral and emotional problems in adolescents with tetralogy of Fallot or a Fontan circulation: a randomized controlled trial.
Dulfer K, **Duppen N**, Blom NA, Van Domburg RT, Helbing WA, Verhulst FC, Utens EM.
Int J Cardiol. 2014 Apr 1;172(3):e425-7.

Systematic review of the effects of physical exercise training programmes in children and young adults with congenital heart disease.
Duppen N, Takken T, Hopman MT, ten Harkel AD, Dulfer K, Utens EM, Helbing WA.
Int J Cardiol. 2013 Oct 3;168(3):1779-87.

Een neonaat zonder anus.
Duppen N, de Blaauw I.
Ned Tijdschr Geneeskd. 2010;154:A790.

Physical activity in adolescents with juvenile idiopathic arthritis.
Lelieveld OT, Armbrust W, van Leeuwen MA, **Duppen N**, Geertzen JH, Sauer PJ, van Weert E.
Arthritis Rheum. 2008 Oct 15;59(10):1379-84.

SUBMITTED FOR PUBLICATION

The effect of exercise training on pulmonary artery wall shear stress in young patients with Fontan circulation.
Duppen N, Cibis M, Wentzel JJ, Bossers SSM, Potters WV, Moelker A, Kapusta L, Hopman M, Helbing WA.
Eur Heart J Cardiovasc Imaging. (in revision).

PhD portfolio

Name PhD student:	Nienke Duppen
Erasmus MC Department:	Erasmus Medical Center – Pediatrics, division of Cardiology
Research School:	COEUR
PhD period:	August 2009 – August 2014
Promotor(s):	Prof dr W.A. Helbing (Erasmus Medical Center)
	Prof dr M.T.E. Hopman (Radboud University Medical Center)
Title of thesis:	Exercise training in children and young adults with congenital heart disease: rationale, effects and impact on quality of life

	YEAR	ECTS
General academic skills		
Research Integrity	2009	0.5
NIHES		
Introduction clinical research	2010	1.5
Biostatistics for clinicians	2010	1.5
Principles of research in medicine	2010	1.5
Clinical trials	2010	1.5
Regression analysis	2012	2
Biostatistics	2012	5.7
Biomedical writing and communication	2012	4
COEUR		
Cardiovascular imaging	2010	1.5
Cardiovascular medicine	2011	1.5
Congenital heart disease	2013	1.5
(Inter)national conferences and presentations		
Fitkids, Zeist, the Netherlands (oral presentation)	2009/2014	0.8
Patient information day PAH, Soest, the Netherlands (oral presentation)	2010	0.4
Sport and congenital heart disease, Munchen, Germany	2010	0.9
Joint scientific sessions SCMR/EuroCMR, Nice, France	2011	1.2
Scientific sessions SCMR, Orlando, USA	2012	0.9
Pediatric Clinical Exercise Testing, Utrecht, the Netherlands (poster)	2012	0.6
Sport and congenital heart disease, Munchen, Germany (oral presentation)	2012	0.6
World congress of paedatric cardiology and cardiac surgery, Kaapstad, South Africa (poster presentation)	2013	2
AEPC working group Psycho-social care, Cologne, Germany (oral presentation)	2013	1.2
AEPC, London, United Kingdom (poster presentation)	2013	1.2
AEPC, Helsinki, Finland (poster and oral presentation)	2014	1.2

	YEAR	ECTS
Seminars and workshops		
COEUR		
New clinical aspects of heart failure	2009	0.4
Coartation of the Aorta	2010	0.4
PhD day, COEUR	2010-2013	2.4
Congenital heart defects (oral presentation)	2011/2015	0.8
Biomechanics	2012/2014	0.4
Biomarkers	2012	0.4
Gender differences	2013	0.4
Debate, COEUR	2014	0.4
NHS (Dutch heart Foundation)		
Cardiac Function and Adaptation, NHS	2011	2
Masterclass reporting your research, NHS	2011	0.2
Other		
Advanced imaging for clinicians	2009	0.9
PhD integrity	2010	0.9
PHD day, Erasmus MC	2010/2011	0.8
The why and how of readable articles	2010	0.6
NWO talent day	2011	0.6
Teaching activities: supervising research project from ErasmusMC and Radboud university MC students		
Correlation of activity and heart rate in pediatric congenital heart disease patients	2011	2
Testing cardiorespiratory function in children with Tetralogy of Fallot: using maximal or sub-maximal exercise parameters?	2011	0.5
The effect of a three month training program on patients with a Tetralogy of Fallot or a Fontan-circulation	2012	0.5
Long-term follow up in patients with corrected Tetralogy of Fallot: A multicenter retrospective study (published article)	2012	3
The effect of aerobic exercise training on the atrial function and ventricular diastolic function in patients with corrected Tetralogy of Fallot	2013	1.5
Committee		
COEUR PhD committee	2011-2014	
PhD committee	2012-2014	

About the author

Nienke Duppen was born on April the 16th 1981 in Muiden. She attended the high school Sint-Janslyceum in 's-Hertogenbosch. She received her Gymnasium degree in 1999. Nienke started her medical training in 2000 at the University of Groningen after 1 year of travelling Down Under. She followed an extra-curricular internship at the "under five clinic" in Mangochi Hospital, Malawi in 2003. She followed her regular internships at the Martini hospital in Groningen and the Sint Elisabeth hospital in Willemstad, Curaçao. She concluded her internships at the department of surgery at the Ngwelezana hospital, Kwazulu-Natal, South Africa as well as the neonatology department at the Starship hospital in Auckland, New Zealand. Nienke worked at the department of pediatrics in the Radboud academic center for a year and a half, after which she started her PhD in 2009. The PhD project consisted of a multicenter intervention study, researching the effects of sports in children with a congenital heart disease. She was supervised by Prof. Dr. W.A. Helbing, pediatric cardiologist at the Erasmus Medical Center-Sophia Children's hospital in Rotterdam and Prof. Dr. M.T.E. Hopman, physiologist at the het Radboud University Medical Center in Nijmegen. During her PhD project she was a camp counsellor for adolescents with heart disease, organized by the Dutch Heart Foundation. Nienke enjoys spending her leisure time with friends, rowing and travelling.

At the moment she is employed as a pediatric resident at the Sint Elisabeth hospital in Tilburg.

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DAT IS SPORT

Een paar seconden voor de race.
Je hebt fans. Ze worden hees.
Ze verwachten een sensatie.
Ademhalen. Concentratie.
En dan opeens verstomt hun lied.
Wat er gebeurt, begrijp je niet.
Je sluit ze af. Je gumt ze uit.
De wind steekt op binnen je huid.
Je wordt een suizende orkaan
en het schijnt dat je gaat staan,
Dat je verandert in een vorm,
die gehoorzaamt aan een storm.
Die jou laat doen wat je moet doen.
Je springt. Daar ga je. Kampioen.
En terwijl je toegejubeld wordt
denk je: wég zijn – dat is sport.
Je bent getraind en voorbereid,
maar pas als je precies op tijd
Afwezig bent, leeg, en stil,
doet je lichaam wat je wil.
Word je mee op reis genomen.
Dat is sport. De mooiste dromen
worden aan je toegekend
terwijl ergens anders bent.

E van de Vendel
Uit: *Ik juich voor jou*