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CARDIOPULMONARY FUNCTION, QUALITY OF LIFE AND EFFECTS OF EXERCISE IN CHILDREN AND ADOLESCENTS WITH FONTAN CIRCULATION

Eva Rylander Hedlund

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Cardiopulmonary function, quality of life and effects of exercise in children and adolescents with Fontan circulation

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my father, who loved books

ABSTRACT

Background

Survival of children and adolescents with Fontan circulation has increased over the last decades, and today a large majority survive to adult age. There is increasing concern regarding these children's impaired physical performance and quality of life. Little is known about the impact of exercise on cardiopulmonary function and quality of life in this patient group compared with the impact on healthy children.

Aim

The aims of this thesis were to study activity, physical capacity, lung function, quality of life, and sleep before and after an exercise intervention in patients with Fontan circulation and healthy matched controls. A follow-up, one year after the training programme, was also performed. We wanted to evaluate if physical exercise could improve cardiopulmonary function and also, most importantly, quality of life in this patient group.

Method

Patients with Fontan circulation (n = 30) and healthy controls (n = 25) performed measurements and/or assessments of physical activity including accelerometer recordings, submaximal and maximal exercise capacity, lung function, sleep, and quality of life. All examinations were done prior to and after an individualised endurance training programme for 12 weeks, and also after one year.

Results

Patients with Fontan circulation reported less time in regular physical exercise than healthy controls, though the objectively measured activity was similar. Quality of life was reported significantly lower by the patients and by their parents compared with the controls. After the exercise intervention, submaximal exercise capacity had increased and quality of life was improved for the patients. However, the exercise intervention did not have an impact on maximal exercise capacity for the patients. After one year, patients showed further improvement of submaximal exercise capacity and quality of life was still improved, as after the exercise intervention. Moreover, children with Fontan circulation had impaired lung function and a reduced pulmonary diffusing capacity. Diffusing capacity increased with age in the patients, but less than in the control subjects. Moreover, endurance training improved vital capacity in the patient group. Fontan patients seemed to have a prolonged latency to sleep onset compared with healthy children. Increased time in physical activities seemed to be correlated with better sleep quality in patients with Fontan circulation.

Conclusions

Structured individualized training programmes may improve submaximal exercise capacity, lung function, and quality of life in children with Fontan circulation. Also, the improvement of quality of life appears to remain, one year after the intervention. Increased amount of physical activity may also be beneficial for sleep quality for these patients. The clinical importance of our results is that increased physical activity is likely to be beneficial for cardiopulmonary function, quality of life, and sleep quality in this patient group. Thus, patients with Fontan palliation should be encouraged to regularly engage in individually designed sports and activities. Rehabilitation programmes should include structured individualised endurance training for improved outcome in this group of patients. Impaired health-related quality of life is most likely multifactorial and further research is needed to more fully understand the effects of exercise on cardiopulmonary function, sleep, and quality of life in this patient group. Also, more research is needed on how to individualise recommendations and find optimal regimens for exercise prescriptions from early age for these patients. The important message is, though, to encourage physical exercise for these patients for better health and well-being.

LIST OF SCIENTIFIC PAPERS

I. **Hedlund ER,** Lundell B, Villard L and Sjoberg G. Reduced physical exercise and health-related quality of life after Fontan palliation. Acta Paediatr 2016; 105: 1322-1328.

II. **Hedlund ER,** Lundell B, Soderstrom L and Sjoberg G. Can endurance training improve physical capacity and quality of life in young Fontan patients? Cardiol Young 2018; 28(3): 438-446.

III. **Hedlund ER,** Ljungberg H, Soderstrom L, Lundell B and Sjoberg G. Impaired lung function in children and adolescents with Fontan circulation may improve after endurance training. Cardiol Young 2018; 28(9): 1115-1122.

IV. **Hedlund ER,** Villard L, Lundell B and Sjoberg G. Children and adolescents with Fontan circulation have prolonged sleep onset but physical exercise may improve sleep quality. In manuscript.

CONTENTS

LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
AVSD	Atrio-ventricular septal defect
BP	Blood pressure
DLCO	Diffusing capacity for carbon monoxide
FEF50%	Forced expiratory flow at 50% of FVC exhaled
FEF75%	Forced expiratory flow at 75% of FVC exhaled
FEV1.0	Forced expiratory volume at the end of the first second
FRCPL	Functional residual capacity, plethysmography
$FRCN_2$	Functional residual capacity, Nitrogen wash-out
FVC	Forced vital capacity
HLHS	Hypoplastic left heart syndrome
HR	Heart rate
LCI	Lung clearance index
MVPA	Moderate-to-vigorous physical activity
MCID	Minimal clinically important difference
NYHA	New York Heart Association Functional Classification
PedsQL	Pediatric Quality of Life Inventory 4.0
RR	Respiratory rate
RER	Respiratory exchange ratio
RV	Residual volume
SD	Standard deviation
SEM	Standard error of measurement
Swedcon	The Swedish Registry of Congenital Heart Disease
TCPC	Total cavopulmonary connection
TLC	Total lung capacity
VC	Vital capacity
VE	Minute ventilation
VE/VCO_2	Ventilatory equivalent of carbon dioxide
VCO_{2max}	Maximal elimination of carbon dioxide
VO_{2max}	Maximal oxygen consumption / uptake

QoL	Quality of life
6MWT	Six-minute walk-test

1 INTRODUCTION

Univentricular heart is a rare and complex heart malformation. The incidence has been reported to be 0.39 per 1000 births (1). The survival of children with complex heart malformations has improved and, today, many survive to adult age (2, 3). The survival has improved because of developed surgical techniques over the last decades. Children with univentricular hearts go through repeated surgical interventions, resulting in a Fontan circulation (4-7). With increased survival, there is growing concern about these patients' physical performance, but also about their quality of life.

1.1 ANATOMY

The children in question are born with only one functional ventricle in the heart. There are different underlying malformations to this condition, for example tricuspid or mitral atresia, underdeveloped right ventricle, underdeveloped left ventricle, a genuine single ventricle, or other complex heart malformations that are not possible to surgically correct to a biventricular circulation. Hypoplastic left heart syndrome is a rare malformation. This malformation is severe, with an underdeveloped left side of the heart (Fig 1).

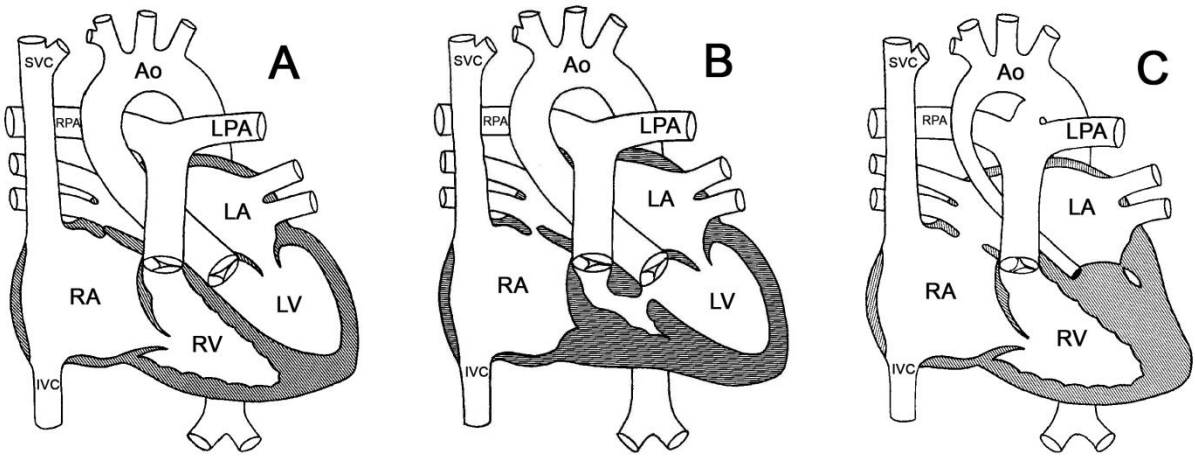

Figure 1. (A) Normal heart. (B) Tricuspid atresia. (C) Hypoplastic left heart syndrome (HLHS). RA = Right atrium; RV = Right ventricle; LA = Left atrium; LV = Left ventricle; SVC = Superior vena cava; IVC = Inferior vena cava; RPA = Right pulmonary artery; LPA = Left pulmonary artery; Ao = Aorta.

1.2 THE FONTAN PROCEDURE

The Fontan operation was first performed in 1968 in a patient with tricuspid atresia and described in 1971 by Fontan and Baudet (6). The procedure bears Fontan's name, but was far from his only accomplishment in the field. Francis Fontan was a cardiac surgeon at the Department of Cardiac Surgery at the University of Bordeaux. He was very successful in many types of surgery for congenital heart malformations and also in heart transplantations. He died in January 2017 at the age of 88.

Initially, the surgical principle was to connect the right atrium to the pulmonary artery, where the right atrium could act as pump for pulmonary circulation. However, this technique had disadvantages, with risk of thrombosis, arrhythmias, and failing pump function. Then, new techniques developed during the 1980s, where the superior vena cava was anastomosed directly to the pulmonary artery and the inferior vena cava was anastomosed to the pulmonary artery with a lateral tunnel technique inside the right atrium. The latest modification of the Fontan operation is using an extracardiac conduit between the inferior vena cava and the pulmonary artery; this is the established technique today (2, 7, 8) (Fig 2). The Fontan surgery is today a staged palliative surgery, where stage I is a palliation in the neonatal period depending on the hemodynamics of the defect. Stage II is the bidirectional Glenn procedure at the age of around six months, where the superior vena cava is anastomosed to the right pulmonary artery. Stage III is when the blood flow in inferior vena cava is directed to the pulmonary circulation by either a lateral tunnel or an extracardiac conduit, as described above, between the ages of two and four years (8).

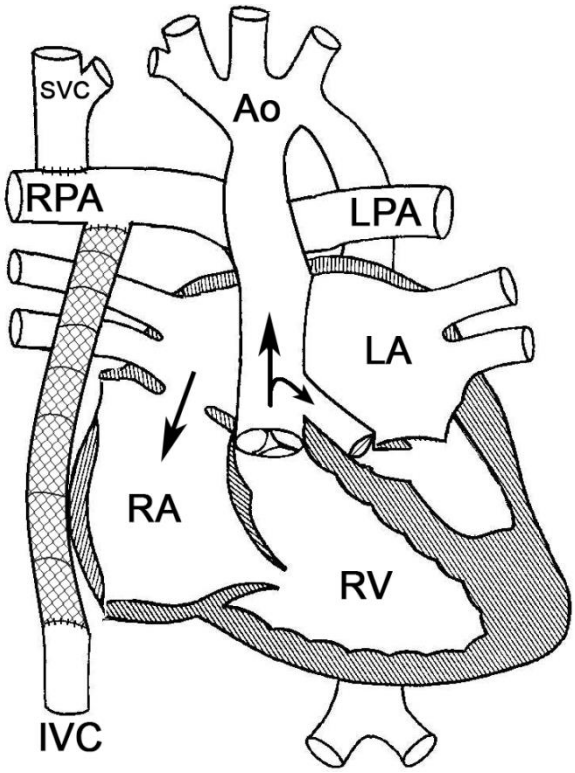

Figure 2. The Fontan procedure with an extracardiac conduit between inferior vena cava and pulmonary artery. RA = Right atrium; RV = Right ventricle; LA = Left atrium; SVC = Superior vena cava; IVC = Inferior vena cava; RPA = Right pulmonary artery; LPA = Left pulmonary artery; Ao = Aorta.

In the Swedish Registry of Congenital Heart Disease, Swedcon (9), there are approximately 400 children registered as living with a total cavopulmonary connection or Fontan circulation in Sweden today, with approximately 100 of these children living in the Stockholm region. The number of adult patients, over the age of 18 years, living with a total cavopulmonary connection in Sweden is approximately 160, with approximately 20 of these in the Stockholm region, according to the registry. According to the same registry, 30 foetuses received a prenatal diagnosis of univentricular hearts between the years 2015–2017 in Stockholm, thus the yearly incidence would be around 10 foetuses. The majority of foetuses diagnosed with univentricular hearts led to a parental decision of abortion after repeated medical counselling during the pregnancy. During the years 2015–2017 there were only five children born with univentricular hearts in the Stockholm region according to the registry.

1.3 THE FONTAN PHYSIOLOGY

In the Fontan circulation, the systemic venous return is redirected to passively perfuse the lungs without a pumping subpulmonary ventricle. Systemic venous pressure and pulmonary vascular resistance are the main determinants of pulmonary blood flow and filling of the ventricle. The absence of a subpulmonary pumping ventricle limits pulmonary blood flow and thus preload to the ventricle. Low ventricular filling and end-diastolic pressure (preload) may reduce cardiac output, especially in response to increased demand during exercise. A fenestration between the systemic veins and the atrium can increase cardiac output, but will lead to oxygen desaturation. Also, an increase in pressure in the systemic veins can be reduced to some extent by a fenestration (10). Patients with Fontan circulation and increased systemic venous pressure may experience serious complications like hepatic fibrosis, protein-losing enteropathy, or plastic bronchitis (7).

Ventricular contractility does not seem to be the main limiting factor for cardiac output in a Fontan circulation, as can be the case in a biventricular circulation. During exercise, a patient with Fontan circulation has limited ability to increase cardiac output by reduced pulmonary vascular resistance and thus increased pulmonary blood flow (10-12). Also, chronotropic function is impaired in this patient group and the reason is probably multifactorial, including factors like surgical scarring and high venous pressure. This will further limit the normal increase in cardiac output during exercise (13). Since the Fontan circulation has limited preload and stroke volume reserve, an increased heart rate may not increase cardiac output as in a biventricular circulation. Tachycardia may actually decrease cardiac output due to a fall in preload of the ventricle. (14)

Patients with Fontan circulation will have a passive pulmonary blood flow, restrictive lung pattern, and low cardiac output. A major determinant of cardiac output in the Fontan circulation is the development and resistance of the pulmonary vasculature (15, 16). The development of the pulmonary vasculature is not normal in Fontan patients. Many factors affect the development, including reduced blood flow, desaturation, collateral flow, lack of pulsatile flow, and absence of high blood flow and pressure during exercise. Also, the pulmonary circulation may have a progressive worsening over time leading to increased pulmonary vasculature resistance and, thus, a failing Fontan circulation (10, 13, 17, 18).

1.4 LONG-TERM OUTCOME

In a review (2) of the Fontan operation over the last five decades, it was shown that there is a trend towards improved prognosis for patients with Fontan circulation, both early and long-term. Children are surgically corrected into a Fontan circulation at a lower age, today, and the extracardiac total cavopulmonary anastomosis has become the most frequently used surgical technique internationally. Early mortality has decreased and the long-term survival has improved. Survival rates reported after 25 and 30 years were 83% (19) and 43% (3), respectively. Common causes of late mortality were ventricular failure, sudden cardiac death, and death after reoperation, including cardiac transplantation. The growing number of patients with Fontan circulation surviving into adult life will lead to more considerations regarding cardiac transplantations. The indication can be ventricular failure, but also hemodynamic failure which can be seen with protein-losing enteropathy. Risk factors for morbidity and mortality must be considered following cardiac transplantation and results vary (2). Adult patients with Fontan circulation can be expected to be in the group with lowest maximal oxygen uptake among adults with congenital heart diseases (20).

A majority of the Fontan patients were reported to be in NYHA (New York Heart Association Functional Classification) (21) functional class I or II. Common complications over time were arrhythmias, thromboembolic events, and protein-losing enteropathy (2). Children with Fontan circulation have been reported to have reduced levels of physical activity (22, 23) and an exercise capacity that is approximately 60–70% of that in healthy children (23-26). Physical activity and exercise in the general paediatric population are accepted to be important preventive measures against acquired cardiovascular disease (27, 28). This has been suggested to be even more important in patients born with congenital heart malformations, a group reported to be less physically active than healthy subjects (22, 23, 29). Reduced oxygen saturation and muscle mass deficiency are other factors that may contribute to reduced physical capacity in Fontan patients (30). Children with Fontan circulation have also been shown to have impaired motor skills and flexibility compared with healthy children (24). Restrictions on activity or exertion by the medical profession and overprotection by parents may limit participation in physical activities alongside healthy peers (31).

The non-pulsatile pulmonary blood flow in children with Fontan circulation might affect pulmonary vasculature. Also, the surgical interventions may have a negative impact on lung development. Studies have showed that the affected lung function in these patients was

correlated with an impaired exercise performance (32). It has also been reported that children with Fontan circulation have a lowered alveolar diffusing capacity (33-36), but more research is needed regarding lung function in this patient group.

Patients with Fontan circulation might experience an affected quality of life (37). Studies have reported a negatively affected quality of life (37-43) and reduced exercise performance even in patients without severe complications during surgical procedures and medical follow-ups (23, 25, 26, 30). Also, it has been shown that patients with Fontan circulation have a lower quality of life compared with patients with less severe heart defects (38). In a recent study (24), it was shown that patients with Fontan circulation had decreased physical performance, but similar quality of life compared with healthy subjects. Atz et al. (44) have presented data showing that exercise performance decreased over time in survivors with Fontan circulation, which was associated with poorer functional health status measured using the Pediatric Quality of Life Inventory (PedsQL). In patients with Fontan circulation, factors such as the type of pumping ventricle, the number of surgical procedures and complications, age at completed Fontan circulation, and arrhythmia have also been reported to influence health-related quality of life (37). A clinical problem, raised by patients and their parents, is disturbed sleep and daily fatigue. In addition, long recovery time with fatigue after physical exercise is reported by patients and/or their parents.

Since research has shown that exercise performance decreases over time in children with Fontan circulation, as well as being associated with poorer functional health status (44), this thesis has focused on providing these patients with an exercise intervention aiming at enhancing or preserving exercise capacity, but also quality of life. Other studies have been performed on children with Fontan circulation concerning effects of exercise. These have shown that exercise is safe and beneficial for physical performance among these patients (45-47) and that exercise may be beneficial for physical performance over longer time (48). Exercise training may, also, have a positive effect on peripheral muscles in children with congenital heart disease (49). Rehabilitation programmes can also enhance physical activity levels in children with Fontan circulation (50). Performing exercise tests, taking part of exercise interventions, and seeing that physical activity is safe, is of importance for patients and their parents (51). Studies have reported that exercise can be beneficial for quality of life in patients with congenital heart disease (51-53); however, these studies had small patient numbers and/or lacking controls.

Knowledge is limited about participation in sports and how exercise is perceived among patients with Fontan circulation. Also, not much is known regarding impact of endurance

exercise on physical capacity and quality of life in these patients and healthy controls. No published study can be found on effects of endurance training programs on lung function, including complete spirometry and measurements of pulmonary diffusing capacity, and also exercise capacity, in these patients and healthy controls. In addition, there are no available studies on sleep patterns in children with Fontan circulation and healthy control subjects. This thesis will contribute with knowledge about physical performance, lung function, sleep, quality of life, and impact of physical exercise in children with Fontan circulation compared with healthy controls. The results and possible effects on cardiopulmonary function, sleep, and quality of life can help healthcare providers to support patients and their parents through developed rehabilitation programmes that should include individually tailored physical exercise.

2 OBJECTIVES

2.1 GENERAL OBJECTIVES

The general objectives of this thesis were to study physical activity, physical capacity, lung function, quality of life, and sleep and see effects of an individualized endurance training programme in patients with Fontan circulation and healthy matched controls. We also performed a 1-year-follow-up after the training program to study long-term effects of physical exercise in these two groups.

2.2 SPECIFIC OBJECTIVES

- To compare self-reported physical exercise with objectively measured accelerometer activity and quality of life among children with Fontan circulation and healthy control subjects. (Paper I)
- To see if an exercise intervention could improve exercise performance and quality of life in children with Fontan circulation, and if the effect could be long-lasting. (Paper II)
- To assess lung function and see if endurance training could improve lung function in children with Fontan circulation compared with healthy children. (Paper III)
- To study sleep and see if endurance training could improve sleep and sleep quality in children with Fontan circulation. (Paper IV)

3 MATERIAL

We considered all children and adolescents with a Fontan circulation, born 1990-2005, in the Stockholm area, (N = 53), for participation in the study. Exclusion was done after reviewing of hospital charts (N = 13) or the families had denied joining the study (N = 10). Exclusion criteria were neurodevelopmental disorder (n = 5), heart transplant (n = 2), being under investigation for further surgery (n = 1), acute myocarditis (n = 1), muscle weakness (n = 1), having moved away from Stockholm region (n = 2), and height below 125 centimeters (n = 1) (Fig 3). The included patients were to propose a healthy friend of same age and gender. These control subjects could not have a chronic disease in an unstable condition that required regular medications or be under medical investigation for unaddressed symptoms.

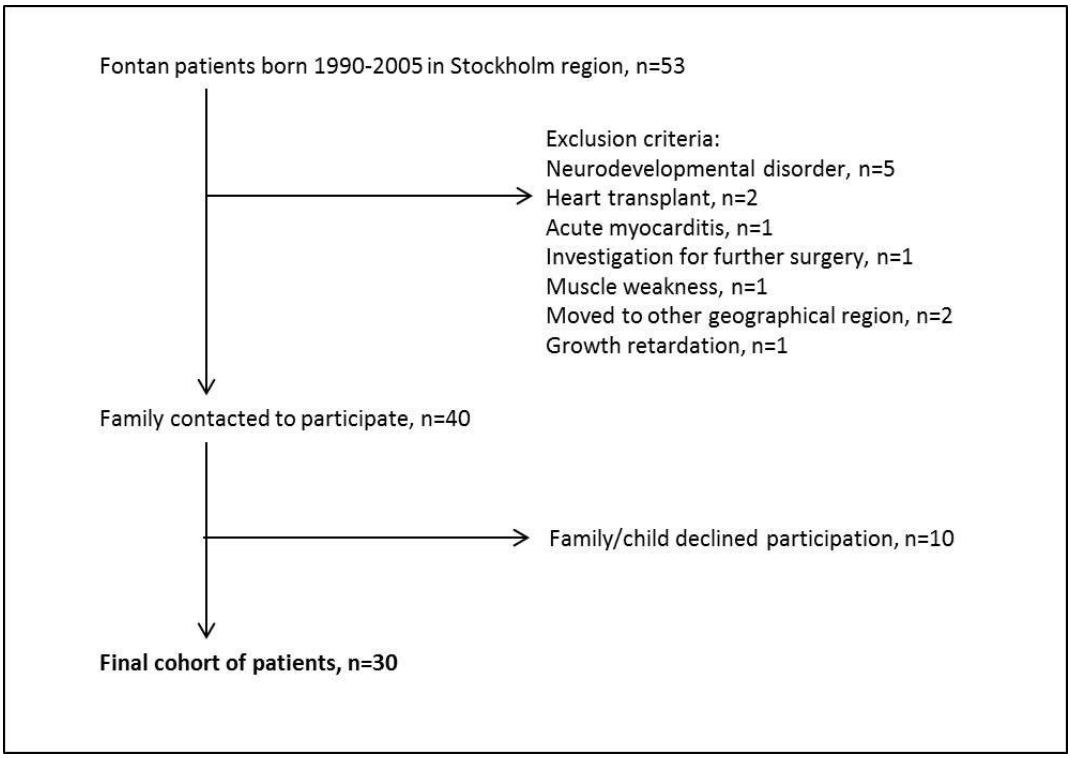

Figure 3. Patient recruitment. Reused with permission from publisher.

Our final cohort consisted of 30 patients with Fontan circulation, after parental consent and child assent. 17 patients proposed a friend of same age and gender, to serve as control subject. 13 patients did not want to ask a healthy friend to be a control subject. Therefore, we recruited 8 matched control subjects from families of staff at the hospital. This resulted

in a total of 25 healthy control subjects. Gender distribution, age, weight, height, and body mass index were similar between patients and controls, see Table 1. Cardiac diagnoses are presented in Table 1. Three patients had pacemakers with epicardial leads, as bradycardia protection, due to sinus node dysfunction. Anticoagulation treatment were aspirin (N = 28) or warfarin (N = 2). 19 patients had either enalapril or captopril prescribed. All patients had an extracardiac Fontan circulation that had been completed at median age 2.4 (1.1–6.4) years. No fenestrations were present in any patient.

Table 1. Characteristics of patients and controls

	Patients	Controls	*p*
Number, N	30	25	
Male/Female, N	16/14	13/12	0.92
Age (years)	14.2 ± 3.2 (8.9-20.4)	13.6 ± 3.5 (8.9-19.0)	0.49
Weight (kg)	43.9 ± 11.8 (24-62)	49.1 ± 16.0 (28.0-89.0)	0.17
Height (m)	1.53 ± 0.14 (1.28-1.78)	1.57 ± 0.16 (1.32-1.86)	0.29
BMI (kg/m^2)	18.3 ± 2.2 (14.6-24.2)	19.2 ± 3.3 (15.3-27.2)	0.22
Cardiac diagnosis	20 hypopl right ventricle		
	9 hypopl left ventricle		
	1 unbalanced AVSD		
Age at Fontan (years)	2.7 ± 1.3 (1.1-6.4)		
Years since Fontan	11.4 ± 3.2 (6.1-16.0)		

Values are presented as Mean ± 1SD (Min-Max)

AVSD: Atrio-ventricular septal defect

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Poweranalysis was performed before inclusion of subjects as regards maximal oxygen uptake, since there were reference values available for this patient group (45). To detect a difference of 10% in mean value for the groups, a power of 0.92 was found with N = 35 and a power of 0.89 was found with N = 25 (p = 0.05). The entire cohort in the Stockholm region was included, but a power >0.80 was reached already with N = 25 in both groups.

Permission was not given from the Ethical Review Board at Karolinska Institutet, Stockholm, (Dnr 2018/128-32) to review medical charts for patients who were excluded or

declined participation in order to describe the representativeness of our cohort. From listings at the Paediatric Cardiology Department at Karolinska University Hospital in Stockholm, Sweden, information about some characteristics was available for these patients. In the group that was excluded, there were 13 patients born between 1990–2005, including six boys and seven girls. In the group of patients and families who declined participation, there were 10 patients born between 1990–2005, with equal numbers of boys and girls. Thus, the groups that were excluded or declined participation had even gender distribution and the same age range as the study participants.

4 METHODS

4.1 STUDY DESIGN

Measurements of physical activity, physical capacity, lung function, sleep and quality of life were performed and retested after an individualized endurance training programme for twelve weeks. Also, a follow-up was done one year later. After the endurance training programme, no specific advises were given regarding continued exercise (Fig 4). All measurements were done similarly and with same intervals for patients and controls.

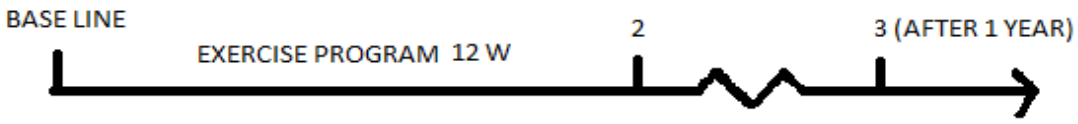

Figure 4. Study design

4.2 PHYSICAL ACTIVITY

4.2.1 Self-reported physical exercise

Subjective measures of physical activity include a variety of activity diaries, proxy reports, and self-administered or interviewer-based questions. A subjective self-report measure is an inexpensive way to assess physical activity. The limitations of self-reported measures are, for example, subjectivity, social desirability, and recall biases (54).

We interviewed patients and controls separately, with respective parent/s present, regarding frequency, duration, and perceived intensity of organised activities and sports during an average week in the three months preceding the study. This included organised physical exercise on a regular basis every week, with an adult leader present. This information was included in the data as self-reported physical exercise. The types of exercise reported included for example physical education classes in school, swimming, horse riding, gymnastics and dancing. The total duration in minutes was reported, as well as the average perceived exertion during the activities evaluated with the Borg scale (55). The Borg scale is a scale from 6-20 and can be used to quantify activity efforts by a subject. The scale has been validated in children with and without structural heart defects (56). Thus, the interview-based questions in our studies allowed us to assess information about different types of regular and organised physical exercise with an adult leader present. The purpose of self-reported physical activity, where information about context and types of activities are given, made it therefore valuable to include in our studies.

There is no standard questionnaire in the clinical setting on participation in physical activities for these patients today. An example of an instrument to measure children's physical activity is the World Health Organization's Health Behaviour in School-aged Children (HBSC) survey. The survey has brief questions about frequency and duration of physical activities, but does not include information regarding perceived exertion during the activities. It does not clearly indicate what type of activities should be reported; organised and/or non-organised. Also, it has been shown that the survey has less reliability and validity in young children and adolescents. In addition, it has not been evaluated in a Swedish population (57). Another questionnaire, the International Physical Activity Questionnaire (IPAQ), has been shown to be difficult for children and adolescents to understand and to fail in giving reliable results (58). Also, IPAQ should primarily be used to evaluate physical activity at a national and international level and is not recommended to use for evaluating physical activity before exercise prescriptions and to evaluate exercise interventions for individuals (58). Thus, these two questionnaires did not suit our patient group or the research questions of our studies.

4.2.2 Objectively measured physical activity

Objective measurements of physical activity, with for example accelerometers, are recommended for children and adolescents, who have a different pattern of physical behaviour than adults (59). In the present studies, physical activity was therefore measured

objectively using accelerometers, in addition to the self-reported information regarding physical exercise. Actigraph GT3X accelerometers (Actigraph, Pensacola, Florida, USA) were used to record daily activity for seven consecutive days and nights during a regular school week. Triaxial accelerometers measure accelerations from three axes and give information about the total duration and intensity of physical activities. A faster acceleration results in a higher intensity and higher counts for the activity. (60, 61)

The accelerometer was attached to the non-dominant wrist (62). After the recording period, the data was downloaded as 60-second epochs to the ActiLife 6 analysing software (Actigraph, Pensacola, Florida, USA). The total vector magnitude in counts was calculated from the three axes as $\sqrt{(axisX^2+axisY^2+axisZ^2)}$. The activity intensity was analysed and categorised in accordance with Evenson's Actigraph cut-off points, which have been shown to provide the most accurate classification for all levels of physical activity intensity in children and adolescents. Activities were classified as sedentary (0–100 counts), light (101–2,295 counts), moderate (2,296–4,011 counts) or vigorous (4,012 counts–above) intensity (63, 64).

The seven-day monitoring with accelerometers in the study population provided reliable measurements of physical activity and activity patterns. It was important to include both weekdays and weekends, as children and adolescents have been shown to have different levels of activity on different days (61). The epoch length used when analysing accelerometer data was 60 seconds in this study. A shorter epoch length could have included more short episodes of moderate-vigorous intensity (60). However, when tested, there was very little difference in the moderate-vigorous activity recorded between different epochs of 15–60 seconds. The time of year when the accelerometer recordings were made may also be an important consideration, but was the same for all patients and controls in our study.

4.2.3 Endurance training programme

Exercise training programmes, including endurance training, were constructed for all participants with regard to self-reported physical exercise at baseline, results from the cardiopulmonary exercise test, as well as season of year, the child's own interests, and available sports facilities in the home environment. The idea of individually made exercise programmes was that it might increase compliance and, hopefully, help the child to continue with physical exercise at the end of the study. In addition to baseline activities, a contract was established between the families and the researchers to include 2 x 45 minutes of additional

organised endurance training every week for 12 consecutive weeks with adult leader present. Sutherland et al. (46) did a review of studies on effects of exercise training in patients with Fontan circulation and concluded that exercise programmes should be at least two months long with at least twice weekly training sessions in order to have positive effects on physical performance. Thus, with this knowledge, the exercise programmes were structured as three-month programmes with twice weekly training sessions.

The exercise programmes could include sports like, for example, football, swimming, horse riding, dancing etc. The instruction was to perform exercises at submaximal level and increase load during the programme. All individually designed programmes were documented and each child received a logbook containing the consented training programme at the top, and spaces below where the subject was instructed to write down every occasion of exercise during the exercise programme, including type of activity, duration, and intensity on the Borg scale (55). Also, all subjects received information to bring their logbook to the planned follow-up visit at the end of the training programme, in line with recommendations for prescription of physical activity (65).

Individually designed training programmes where both children and parents are involved in deciding the type of exercise are important for higher success rate and better compliance. In order to design individual training programmes, information regarding type, duration, and intensity of the physical activities at baseline was registered. This was important since the included children had different exercise experiences, interests, and capacities at the time of inclusion in the study (65).

4.3 EXERCISE CAPACITY

4.3.1 Walk-test

The participants performed a six-minute walk-test (6MWT) at the hospital. The six-minute walk-test is an accessible method to evaluate submaximal exercise capacity in children. The test has been performed by young children from four years of age with reliable results (66). Moreover, it is an established test for exercise capacity in children with heart conditions. The test reflects the subject's ability to perform daily activities and patients with cardiac disease may find them easier to perform than maximal exercise tests (67). In addition, it has been shown that walking distance is correlated to maximal oxygen uptake in maximal cardiopulmonary exercise tests (67).

It is a reliable and reproducible test to use in follow-up of functional capacity and has been shown to detect possible improvements after rehabilitation programmes in children with

congenital heart disease. In order to evaluate effects of exercise training, it is important to choose tests at intensities that are comparable to intensities included in the training programme exercises. (67) It has also been suggested that patients with Fontan circulation may be more limited in performing at maximal than at submaximal level (68). Thus, we chose to evaluate the exercise intervention with tests for both maximal and submaximal exercise capacities, since the training programmes and intensities differed among the participants.

The participants were instructed to walk on an indoor lane as fast and far as possible during six minutes. Variable speed was allowed, but not running. All tests were supervised and structured encouragement and information regarding time left were given by study leaders. At the end of the test, distance that the child had walked during the six minutes was recorded. Heart rate was analysed before and directly after, as well as at two and four minutes after finishing the test. 6MWT was performed before the ergometer cycle test for maximal exercise capacity for each child.

There are no available reference values on the six-minute walk-test in Swedish children and adolescents. In order for reliable comparisons with healthy children, similar age, weight, and height are important factors, since they influence the results in a six-minute walk-test (69). Our patient and control groups had similar age, weight, and height, as described under ‘Material’.

There are no previous studies available on determining minimal clinically important difference (70) for the six-minute walk-test in patients with Fontan circulation. The minimal clinically important difference represents the smallest improvement of importance for the patient. Also, it is used to determine the effectiveness of and satisfaction with a treatment or intervention, as a complement to statistically significant changes that may be of no importance to the health or quality of life of the patient (70). Schrover et al. (71) made a review of studies on minimal clinically important difference in the six-minute walk-test for respiratory, cardiovascular and musculoskeletal diseases. This review found a mean minimal clinically important difference for the six-minute walk-test of 7% change (range 3–15 %) using anchor-based methods, i.e., when a clinical measure is compared with a change in a patient-reported outcome. The minimal clinically important difference in absolute values ranged from 11–54 meters in the same studies. However, the concept of minimal clinically important difference has limitations since it can be determined in various ways (70). We included measurements of quality of life in our research, in order to measure effects of

exercise interventions on exercise capacity in relation to effects on quality of life in both patients and healthy controls.

4.3.2 Cardiopulmonary exercise test

All participants performed symptom-limited exercise tests with a stationary, calibrated upright cycle ergometer (Monark Ergomedic 839E, Monark Exercise AB, Vansbro, Sweden). A ramp-protocol was used, with a continuous progressive increase in load. The cycle ergometer was connected to a testing system (GE CASE Exercise testing system, Davis Medical Electronics Inc., Vista, CA, USA). The cycle ergometer was calibrated once a year to a known weight, in accordance with the manufacturer's specifications. Metabolic variables, including oxygen uptake (VO_2) and respiratory parameters, were analysed breath-by-breath continuously (V-max®, Vyaire Medical, Mettawa, IL, USA), using a mouth-piece and a nose clip to prevent air leakage (Fig 5). Prior to every test, the mass flow meter was calibrated with a fixed volume and the gas analyser with two reference gases.

Before starting the test, start load and continuous increase of load during the test were decided with regard to self-reported baseline activities and for each participant to reach maximal effort in ten minutes. Weight (kg) and height (m) were also included in the data. Echocardiography was done on all subjects, before starting the test, to identify signs of thrombosis, intracardiac shunting, or valvular incompetence of importance.

During the test, the participant received instructions to perform constant pedalling with a rate of 60 rpm (revolutions per minute). Standard 12-lead electrocardiogram, blood pressure, and pulse oximetry were monitored before, during, and for ten minutes after finishing. Blood pressure was measured with cuff and radial artery Doppler signals. The participant was encouraged to continue until maximal exhaustion. Data for maximal oxygen uptake, adjusted for weight in kg, was analysed by averaging oxygen consumption during the last twenty seconds of each test ($\dot{V}O_{2max}$, $ml \cdot min^{-1} \cdot kg^{-1}$).

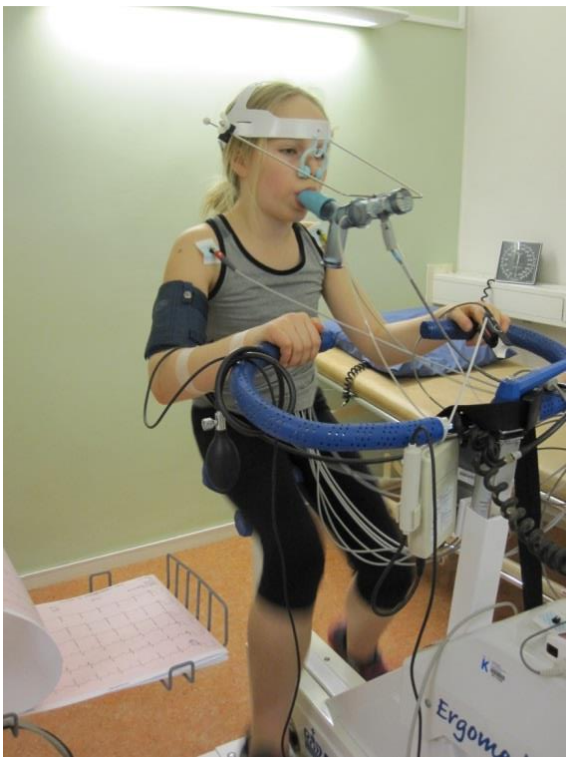

Figure 5. Cardiopulmonary exercise testing including measurement of maximal oxygen uptake. Picture used with permission from study subject.

Since exercise capacity have been shown to decline over the last decades in the general paediatric population in Sweden (72), we chose to compare our patients' results to a healthy matched control group rather than old reference materials.

4.4 LUNG FUNCTION

Spirometry, including measurements of static and dynamic volumes and flows, was done using body plethysmography (V-max®, Vyaire Medical, Mettawa, IL, USA) with the participant at rest in the sitting position. A nitrogen gas multiple breath washout study was also performed and the subject inhaled 100% oxygen to wash out to a nitrogen concentration of 1/40. Then, functional residual capacity was analysed.

Single-breath diffusing capacity was tested with carbon monoxide. After inhalation of a test gas with a defined concentration of carbon monoxide, the participant held his/her breath for eight to ten seconds. During this time, carbon monoxide diffused over the alveolar membrane. Then, the participant exhaled, carbon monoxide concentration was measured and the diffusing capacity calculated.

All tests were done at least twice, until similar results were achieved, for each participant. Swedish reference values (73-75) were used for lung function tests. System calibrations were made in accordance with the manufacturer's instructions and recommendations once a day, using a known volume and a known pressure in the box for static and dynamic volumes and capacities. Nitrogen ventilation calibration was made with two defined reference gases and ambient air. Calibration of diffusing capacity system was made prior to every test with a standardized test gas.

4.5 SLEEP ANALYSIS

Actigraph GT3X accelerometers (Actigraph, Pensacola, Florida, USA) were used for sleep-wake scoring for seven consecutive nights during a regular school week (76, 77). The accelerometer was attached to the non-dominant wrist in order to improve compliance and also to record isolated arm movements (62, 78). After the recording period, data was downloaded as 60-second epochs to the ActiLife 6 analysing software (Actigraph, Pensacola, Florida, USA). Each participant reported 'In Bed Time' and 'Out of Bed Time' for the seven nights in a diary. Using algorithms developed to distinguish between sleep and wakefulness, analyses of accelerometer recordings could be used to determine sleep variables. The clinical benefit of accelerometers for sleep analysis is the possibility of performing long-term registrations in the individual's own sleep environment and routines (76).

Sleep analyses were performed using ActiLife 6 analysing software (Actigraph, Pensacola, Florida, USA). For sleep analyses, the algorithm developed by Sadeh et al. (79) was used. This algorithm has been validated and showed that sleep-wake scoring from wrist-worn accelerometers in healthy children and adults reached high agreement with traditional polysomnography for sleep periods (76). The Sadeh algorithm uses the y-axis epoch data and scores individual epochs as either sleep or non-sleep. 'In Bed Time' and 'Out of Bed Time' variables were extracted from self-reported sleep diaries for each individual as a complement to the accelerometer-derived analyses based on the algorithm by Sadeh et al..

Total minutes in bed and total sleep time in minutes were analysed. Sleep efficiency (%) was calculated as total sleep time divided by total minutes in bed, i.e., the percentage of epochs categorised as asleep within the total number of epochs in bed. Total counts summarised from the Y-axis during sleep time were also extracted. Latency was analysed as numbers of minutes from 'In Bed Time' to sleep onset. Number of awakenings and average length of awakenings were analysed. If at least ten consecutive minutes were categorised as awake, the

sleep period ended. If an awakening was shorter, it did not interrupt the sleep period. Thus, even though an epoch was categorised as awake, it did not have to be an actual awakening to full consciousness of the subject. Wake after sleep onset was analysed and defined as the total number of minutes the subject was defined as awake during the sleep period. Sleep variables analysed are summarised in Table 2.

Table 2. Sleep variables

In Bed Time (hh:mm)	Time when subject goes to bed
Out of Bed Time (hh:mm)	Time when subject gets out of bed
Total minutes in bed (min)	Total minutes between 'In Bed Time' and 'Out of Bed Time'
Total sleep time (min)	Total number of minutes scored as 'asleep'
Sleep efficiency (%)	Number of sleep minutes divided by total numbers of minutes the subject was in bed
Total counts night	Total accelerometer counts summed together for the entire sleep period from axis Y
Latency (min)	Numbers of minutes from 'In Bed Time' to sleep onset
Awakenings (N)	Number of different awakening episodes
Average awakening (min)	Average length of all awakening episodes
Wake after sleep onset (min)	Total number of minutes scored as 'awake' after sleep onset

4.6 QUALITY OF LIFE

Quality of life is a multidimensional concept including physical, psychological, emotional, and social functioning. Health-related quality of life is often used as a concept to measure quality of life and how it is affected by disease and treatment in patient populations. It is important to study quality of life as a health care outcome and to evaluate interventions (80).

The definitions of 'Quality of life' and 'Health' from the World Health Organization are as follows:

> Quality of life:
>
> *Quality of Life is an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment.*
>
> *World Health Organization, 1997*

Health:

A state of complete physical, mental and social well-being, and not merely the absence of disease

World Health Organization, 1948

Pediatric Quality of Life Inventory Version 4.0

Pediatric Quality of Life Inventory Version 4.0 (PedsQL) generic core scales (Mapi Research Trust, Lyon, France) was used to study quality of life. The PedsQL generic core scales consists of 8 items of physical functioning (physical domain), 5 items of emotional functioning, 5 items of social functioning, and 5 items of school functioning (psychosocial domain). Each participant and their parents answered separate questionnaires regarding the preceding month. The parental questionnaire assessed the parent's perceptions of their child's quality of life (parental PedsQL score). The parent forms and child forms are identical, but the questions in the parent forms are posed in a third-person tense. Each answer was transformed into a five-step score, ranging from 0-100. The total average score, as well as scores for the physical and psychosocial domains, were calculated. The PedsQL 4.0 instrument is used in the national Swedish registry for congenital heart diseases (Swedcon).

The PedsQL was originally developed for paediatric cancer patients (aged 8-18 years) as well as their parents, at various stages of treatment in the USA. Paediatric cancer patients served as the model for the development of the generic health-related quality of life measure, since these patients have a wide range of symptoms (81). The PedsQL was developed through patient and parent focus groups, interviews with experienced care providers, and review of available literature. It was designed to measure the core health definition by the World Health Organization (WHO), including role functioning, i.e. school for children. There are generic core scales as well as disease-specific modules, such as a cardiac module. Disease-specific modules may generate higher sensitivity for a chronic health condition, whereas a generic instrument allows comparisons between groups including healthy children (82). The PedsQL 4.0 has shown reliability, validity, sensitivity, and responsiveness, as well as feasibility for quality of life assessment in children with acute or chronic health conditions and in healthy children over a broad age range (83).

Research has been performed on a heterogeneous group of children (n = 915) aged 5-18 years and parents to children aged 2-18 years (n = 1,629) who were recruited from scheduled well-

child checks, hospital specialty clinics, or had been seen as inpatients or outpatients at hospital. It showed internal consistency reliability for the total score (α = 0.88 child, 0.90 parent), physical score (α = 0.80 child, 0.88 parent), and psychosocial score (α = 0.83 child, 0.86 parent). Construct validity was shown and confirmed that healthy children reported higher scores than acutely or chronically ill children (82). Also, research has been done to evaluate the PedsQL 4.0 for paediatric health outcome on large cohorts and showed minimal missing responses, excellent reliability, and it distinguished between children with chronic illnesses and healthy children (84). From the age of five, children can reliably and validly report their quality of life with age-appropriate instruments. Also, the parent reports have been shown to be valid and reliable in all age groups (85). Sensitivity shows differences among individual patients or patient groups and responsiveness provides information about changes in individual patients or patient groups over time. Research has shown that PedsQL is sensitive to show significant differences in PedsQL scores with cardiac disease severity and also responsive with significant changes in PedsQL score between visits and follow-ups after treatments (86).

The Swedish translation of the generic module has been studied in a general child population in Sweden with 1,564 children (age 8-14 years) and 634 parents. The translation was done by Dr Varni and the Mapi Research Institute. The generic total core scale showed internal consistency reliability with α = 0.90 child and α = 0.89 parent. It was also showed to be valid and with high agreement in test-retest on overall scores in children and parents (87).

Minimal clinically important difference (MCID) for PedsQL scores was analysed. It was defined as the smallest difference in a score that patients perceive to be beneficial and that would mandate a change. The minimal clinically important difference was analysed by calculating the Standard Error of Measurement (SEM) and one SEM identified the MCID in responsiveness in a health-related quality of life measure. The SEM was calculated by multiplying the standard deviation by the square root of Cronbach alpha reliability coefficient. A 4.4 change in the Total Scale Score for child self-report and a 4.5 change in the Total Scale Score for parent proxy-report were defined as MCID by Varni et al (84). Cut-off points for risk of having impaired quality of life were determined by taking one standard deviation below the population mean (84). Scores at cut-off points represents scores similar to those of children with chronic diseases, e.g., children with newly diagnosed cancer report total score of 68.9 and children with chronic rheumatic diseases report a total score of 72.1 (83).

In the present studies, quality of life was evaluated using the PedsQL 4.0 generic module, in patients and healthy controls before and after an exercise intervention and at follow-up after one year. The PedsQL 4.0 generic core scale has been shown to be useful in clinical practice by paediatric cardiologists for a wide range of heart conditions including complex malformations (88). The instrument has shown validity in a large cohort of children with complex congenital malformations and Fontan palliation, and showed impaired quality of life that may worsen over time, compared with healthy subjects in the PedsQL database (43). We believed that the PedsQL instrument would be a suitable instrument to use because of its reliability, validity and responsiveness. In addition, we chose the generic rather than cardiac module to allow group comparisons with healthy controls.

4.7 STATISTICAL ANALYSES PAPER I-IV

The statistical program used was Statistica 12 (StatSoft Inc, Tulsa, Oklahoma, USA). Statistical significance was set at $p < 0.05$. Descriptive statistics of variables were presented as mean ± standard deviation (SD) when variables were normally distributed and as median (range) when variables were not normally distributed (Paper I-IV).

T-test

This test was used for groups to analyse normally distributed variables.

Chi-square test

This test was used for groups to analyse categorical variables, for example the proportion of males to females between the case and control group.

Mann-Whitney U test

This is a non-parametric test for comparing data from two groups. The test was used to analyse continuous data not normally distributed.

Repeated measures ANOVA

Repeated measures analysis of variance (ANOVA) was used to compare repeated measurement of the outcome variables between the groups, taken before and after the training programme and at follow-up after one year.

Multiple stepwise regression model

Multiple regression analysis was used to examine the extent to which a dependent variable could be explained by a number of independent variables. The variable whose univariable test had a p-value < 0.05 was considered a candidate for the multivariable model. In selecting independent variables into the regression equation, a stepwise method was used. This method adds and subtracts variables until the equation contains only significant variables.

Paper I

Statistical analyses between patients and controls were made using t-tests, chi-square tests or Mann-Whitney tests, as appropriate. Multiple stepwise regression analysis was carried out to identify positive predictors of quality of life scores. Independent variables in the model were having a heart defect, age, gender, weight, height, self-reported physical exercise, total vector magnitude, and time in moderate-to-vigorous activity.

Paper II

Statistical analyses between patients and controls were made using t-tests, chi-square tests or Mann-Whitney tests, as appropriate. Repeated measures ANOVA were made for analyses over time. A multiple stepwise regression model was made with quality of life as a dependent variable and having a heart defect, distance in 6MWT, maximal oxygen uptake, maximal work-load, maximal heart rate, maximal blood pressure and oxygen saturation at maximal effort as independent variables.

Paper III

Statistical analyses between patients and controls were made using t-tests and chi-square tests, as appropriate. Repeated measures ANOVA were made for analyses over time. A multiple stepwise regression model was done with maximal oxygen uptake, $\dot{V}O_{2max}$, as the dependent variable, and gender, having a heart defect, age, weight, height, forced vital capacity (FVC), forced expiratory volume at the end of the first second (FEV1.0), vital capacity (VC), total lung capacity (TLC), residual volume (RV), and pulmonary diffusing capacity (DLCO) as independent variables.

Paper IV

Statistical analyses between patients and controls were conducted using t-tests, Mann-Whitney U-tests and chi-square tests, as appropriate. Repeated measures ANOVA were conducted for analyses over time. A multiple stepwise regression model was done with sleep efficiency as dependent variable, and having a heart defect, gender, age, total vector magnitude, and time in moderate-to-vigorous physical activity as independent variables.

4.8 ETHICAL APPROVAL

The studies were approved by the Ethical Review Board at Karolinska Institutet, Stockholm (Dnr 2010/84-31/4). Permission was not given from the Ethical Review Board at Karolinska Institutet, Stockholm (Dnr 2018/128-32), to go through medical charts for the patients who were excluded or who declined participation in order to describe the selection and representativeness of our cohort.

5 RESULTS

5.1 PAPER I

The objective of Paper I was to compare self-reported physical exercise with objectively measured accelerometer activity and quality of life among children with Fontan circulation and healthy control subjects. We found that the patients reported less time participating in organised physical exercise in minutes per week than controls. Also, the patients reported a lower average intensity for the exercise reported, than the controls (Table 3). Self-reported physical exercise decreased significantly with increasing age in the whole group. The self-selected controls by the patients (n = 17) reported less time in exercise than the other controls (n = 8).

Table 3. Self-reported physical activity and Accelerometry

	Patient	Control	p	Valid N Patient	Valid N Control
SELF-REPORTED ACTIVITY					
Physical activity, minutes per week	113.5±66.1	227.6±147.2	<0.001	30	25
Physical activity, mean intensity in Borg	13.0±2.1	14.3±1.9	<0.05	24	25
ACCELEROMETER					
Total vector magnitude 7 days, counts	$19.2\times10^6\pm4.6\times10^6$	$18.9\times10^6\pm4.7\times10^6$	0.79	30	25
Sedentary %	48.6±4.4	51.8±5.2	<0.05	30	25
Light %	41.1±3.3	38.4±3.6	<0.01	30	25
Moderate %	10.3±4.2	9.8±3.7	0.67	30	25
Vigorous %	0	0		30	25

Values presented as Mean±1SD

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Even though the self-reported activity differed between the groups, the objectively measured total vector magnitude during the seven days was similar in patients and controls (Table 3). Total vector magnitude was not influenced by gender or anatomical functional ventricle. A significant decrease in total vector magnitude was found with increasing age for patients, but not for controls (Fig 6).

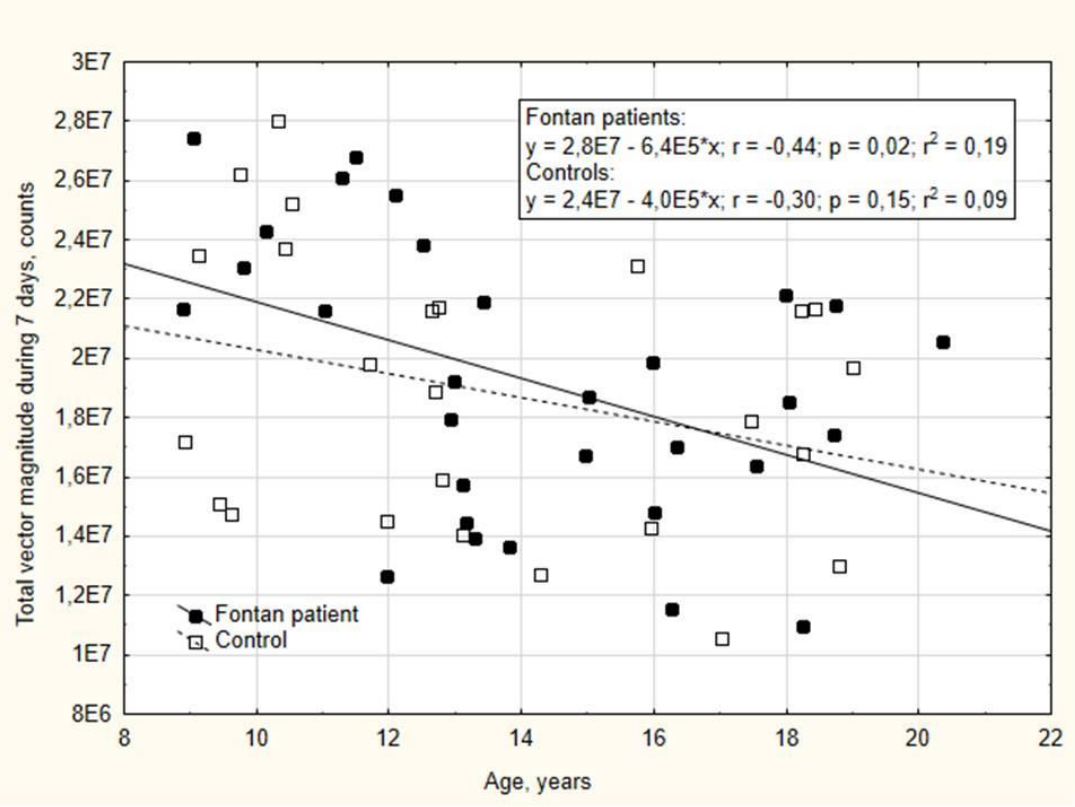

Figure 6. Total vector magnitude during 7 days in counts vs. age in years in patients and controls. Reused with permission from publisher.

Physical activity intensities, according to Evenson's cut-off points, were analysed and are presented in Table 3. The patients had reduced time in sedentary activity and increased time in light activity compared with the controls.

Patients and controls had similar amounts of time in moderate-to-vigorous physical activity (MVPA) in minutes during the seven-day recording (1,035 ± 420 minutes versus 989 ± 377 minutes, p = 0.67). An accepted daily minimum recommendation for young people is an average MVPA of 60 minutes per day (27, 89). This was achieved by almost all patients and controls, excepting only three patients and two controls.

Quality of life

The total PedsQL scores were significantly lower for patients than controls. The parents' PedsQL scores were also lower for patients than controls. Similar differences were found for the physical and psychosocial domains (Table 4). The PedsQL scores were not influenced by gender or age. The controls brought by Fontan patients had significantly lower PedsQL

scores than the other controls (83.4 ± 8.1 versus 90.8 ± 5.2, $p < 0.05$). When the results from the two control groups were compared with Swedish reference material (87), the self-selected controls by the patients had a lower PedsQL scores ($p < 0.05$), while the controls recruited by the research team had similar PedsQL scores. When analysed using a multiple stepwise regression model, positive predictors of quality of life were not having a heart malformation and more time spent in self-reported physical exercise.

Table 4. Quality of life

	Patient	Control	p	Valid N Patient	Valid N Control
PEDSQL, score 0-100					
PedsQL Children Total	**70.9 ± 9.9**	**85.7 ± 8.0**	**<0.001**	**30**	**25**
PedsQL Children - Physical	68.6 ± 14.2	89.6 ± 10.1	<0.001	30	25
PedsQL Children - Psychosocial	72.2 ± 9.8	83.7 ± 9.7	<0.001	30	25
PedsQL Parent Total	**65.1 ± 18.0**	**89.2 ± 8.2**	**<0.001**	**30**	**24**
PedsQL Parent - Physical	68.8 ± 20.5	93.8 ± 8.2	<0.001	30	25
PedsQL Parent - Psychosocial	63.2 ± 18.3	86.9 ± 9.8	<0.001	30	24

Values presented as mean ± 1SD

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5.2 PAPER II

The objective of Paper II was to study if endurance training could improve physical capacity and quality of life in children after Fontan palliation, and if the effect could be long-lasting.

At the second visit, only one patient had not followed the 12-week training programme. Furthermore, one patient and two control subjects did not want to return for the follow-up after one year. As described in Paper I, patients reported less time in organised physical exercise per week with a lower average intensity and a lower quality of life than controls at baseline.

6-minute walk test

At baseline, patients walked a significantly shorter distance in the 6MWT than the controls (591 ± 66 vs. 678 ± 61 meters, $p < 0.001$) (Table 5). Heart rate directly after six minutes of walking and heart rate recovery were similar in patients and controls. In a study from Switzerland (69), 496 healthy children and adolescents aged 5-17 years walked a mean

distance of 618 ± 79 meters. To our knowledge, there is no available Swedish reference material for the 6MWT. Our healthy children walked a longer distance ($p < 0.001$), while our patients walked a similar distance ($p = 0.06$) compared with the Swiss reference material, but the mean age was lower in the Swiss reference material and comparison with reference material from other countries may not be valid.

Table 5. Characteristics and Results

	1. BASELINE			2. AFTER TRAINING 12 WEEKS			3. FOLLOW-UP 1 YEAR		
	Patients	**Controls**	**p**	**Patients**	**Controls**	**p**	**Patients**	**Controls**	**p**
Number, N	30	25		29	25		28	23	
Female/male, N	14/16	12/13	0.92	13/16	12/13	0.82	12/16	11/12	0.72
Age (years)	14.2 ± 3.2	13.6 ± 3.5	0.50	14.5 ± 3.2	13.9 ± 3.5	0.53	15.1 ± 3.2	14.6 ± 3.4	0.60
Weight (kg)	43.9 ± 11.8	49.1 ± 16.0	0.17	45.4 ± 12.1	50.7 ± 16.0	0.17	47.6 ± 12.4	51.9 ± 14.5	0.26
Height (m)	1.53 ± 0.14	1.58 ± 0.16	0.29	1.54 ± 0.14	1.59 ± 0.16	0.26	1.57 ± 0.14	1.62 ± 0.15	0.29
PedsQL Child	70.9 ± 9.9	85.7 ± 8.0	<0.001	75.3 ± 9.7	87.5 ± 6.6	<0.001	74.8 ± 12.5	84.9 ± 11.2	<0.05
PedsQL Parent	65.1 ± 18.0	89.2 ± 8.2	<0.001	72.7 ± 14.6	88.2 ± 9.9	<0.001	70.2 ± 18.2	86.3 ± 14.4	<0.05
Self-reported exercise									
Minutes per week	113.5 ± 66.1	227.6 ± 147.2	<0.001	168.3 ± 92.7	296.4 ± 185.3	<0.01	122.3 ± 89.7	312.3 ± 225.6	<0.001
Average intensity, Borg	13.0 ± 2.1	14.3 ± 1.9	<0.05	14.0 ± 2.0	14.6 ± 1.4	0.19	11.9 ± 5.4	14.1 ± 3.8	0.11
6MWT (m)	590.7 ± 65.5	678.1 ± 61.2	<0.001	611.8 ± 70.9	699.2 ± 65.1	<0.001	633.4 ± 75.8	688.3 ± 70.8	<0.05

Values presented as mean ± 1SD
PedsQL = Pediatric Quality of Life Inventory Version 4.0
6MWT = 6-minute walk test

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Cardiopulmonary exercise testing

All patients had sinus rhythm during the maximal exercise tests. No complications or arrhythmias of importance were detected in any patient. At rest, heart rate and systolic blood pressure were similar in patients and controls. However, oxygen saturation at rest was significantly lower for patients than controls (95 ± 3 % vs. 98 ± 1 %, $p < 0.001$). During the exercise tests, patients reacted with a lower increase of heart rate ($p < 0.001$) and a lower increase of blood pressure ($p < 0.05$) than the controls. The patients also reacted with a significant decrease in oxygen saturation ($p < 0.001$).

At baseline, maximum work-load and maximal oxygen uptake, $\dot{V}O_{2max}$, were lower for patients than controls. Maximal carbon dioxide elimination, $\dot{V}CO_{2max}$, was significantly lower for patients than controls, while ventilatory equivalent for carbon dioxide, VE/VCO_2, at maximal effort was significantly higher (Table 6). VE/VCO_2 is a measure of the relationship between minute ventilation and carbon dioxide elimination. It is a measure of ventilatory efficiency, but has not been studied as thoroughly in paediatric populations as in adult populations, where a high VE/VCO_2 indicates a worse prognosis (90).

We found that oxygen pulse, a surrogate measure of stroke volume, was significantly lower at maximal effort smaller in our patients than controls (9.7 ± 2.9 vs. 11.7 ± 3.8 ml·beat^{-1}, $p < 0.05$). Oxygen pulse is oxygen uptake, VO_2, divided by heart rate and has been shown to be a valid estimate of stroke volume during maximal exercise in healthy adolescents (91).

Table 6. Results from cardiopulmonary exercise testing at maximal effort

	1. BASELINE			2. AFTER TRAINING 12 WEEKS			3. FOLLOW-UP 1 YEAR		
	Patients	**Controls**	**p**	**Patients**	**Controls**	**p**	**Patients**	**Controls**	**p**
HR max (beats·min-1)	166 ± 20	191 ± 10	<0.001	168 ± 20	192 ± 9	<0.001	169 ± 19	194 ± 8	<0.001
BP max (mmHg)	146 ± 14	161 ± 16	<0.001	150 ± 17	160 ± 15	<0.05	152 ± 14	160 ± 16	<0.05
Oxygen saturation at maximal effort (%)	91 ± 4	98 ± 1	<0.001	91 ± 4	97 ± 1	<0.001	92 ± 4	97 ± 1	<0.001
RR max	49 ± 7	49 ± 11	0,86	50 ± 10	51 ± 11	0.61	51 ± 8	52 ± 10	0.78
RER	1.05 ± 0.08	1.11 ± 0.08	<0.01	1.07 ± 0.05	1.11 ± 0.08	<0.05	1.08 ± 0.08	1.12 ± 0.08	0.12
Maximum work load (watts·kg-1)	2.3 ± 0.4	3.0 ± 0.7	<0.001	2.3 ± 0.4	3.1 ± 0.7	<0.001	2.3 ± 0.4	3.2 ± 0.8	<0.001
VO2max (L·min-1)	1.55 ± 0.43	2.11 ± 0.70	<0.001	1.59 ± 0.43	2.30 ± 0.79	<0.001	1.66 ± 0.49	2.36 ± 0.78	<0.001
V̇O2max (ml·min-1·kg-1)	35.0 ± 5.1	43.7 ± 8.4	<0.001	35.6 ± 6.3	45.7 ± 9.4	<0.001	35.2 ± 5.9	45.8 ± 9.9	<0.001
V̇CO2max (ml·min-1·kg-1)	36.6 ± 6.3	48.1 ± 10.2	<0.001	37.9 ± 7.1	50.3 ± 9.4	<0.001	37.8 ± 6.0	50.2 ± 8.9	<0.001
V̇Emax (L·min-1·kg-1)	1.43 ± 0.26	1.50 ± 0.34	0,44	1.48 ± 0.28	1.58 ± 0.34	0.23	1.54 ± 0.28	1.59 ± 0.33	0.56
VE/VCO2	39.0 ± 4.3	30.8 ± 3.6	<0.001	39.2 ± 4.6	31.3 ± 3.6	<0.001	40.8 ± 5.3	31.6 ± 3.9	<0.001

Values presented as mean ± 1SD

HR = Heart rate
BP = Systolic blood pressure
RR = Respiratory rate
RER = Respiratory exchange ratio
V̇O2max = Maximal oxygen uptake
V̇CO2max = Maximal elimination of carbon dioxide
VE = Minute ventilation
VE/VCO2 = Ventlatory equivalent for carbon dioxide

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Effects of endurance training program

Both groups had increased weekly duration of exercise after the exercise intervention (from 113.5 ± 66.1 to 168.3 ± 92.7 minutes per week for patients and from 227.6 ± 147.2 to 296.4 ± 185.3 minutes per week for controls) (Table 5). After one year, patients had decreased duration of exercise, down to the levels before the intervention, while controls had similar amount of duration of exercise, as to that after the intervention. After the intervention, patients had increased average intensity for all activities, while the controls had similar average intensity throughout the study (Table 5). After one year, patients had similar intensity on the Borg scale as after the intervention (median Borg 14.0 (10.0–17.5) after intervention

vs. median Borg 14.75 (7.5–17.0) at follow-up after one year). Values in Table 5 presented as mean ± SD.

6-minute walk-test

The patients walked longer distances in a six-minute walk-test after the exercise intervention ($p < 0.05$), while the controls did not. After one year, the patients walked even longer distances than after the intervention ($p < 0.05$), while the controls still had unchanged distances (Table 5). Heart rate after the walk-test was similar to that before the intervention for patients and controls.

Cardiopulmonary exercise testing

After the exercise intervention, patients did not increase their maximum work-load or maximal oxygen uptake, $\dot{V}O_{2max}$, as the controls did ($p < 0.05$). After one year, both groups had unchanged maximum work-loads and maximal oxygen uptake, $\dot{V}O_{2max}$, as to after the intervention (Table 6 and Fig 7).

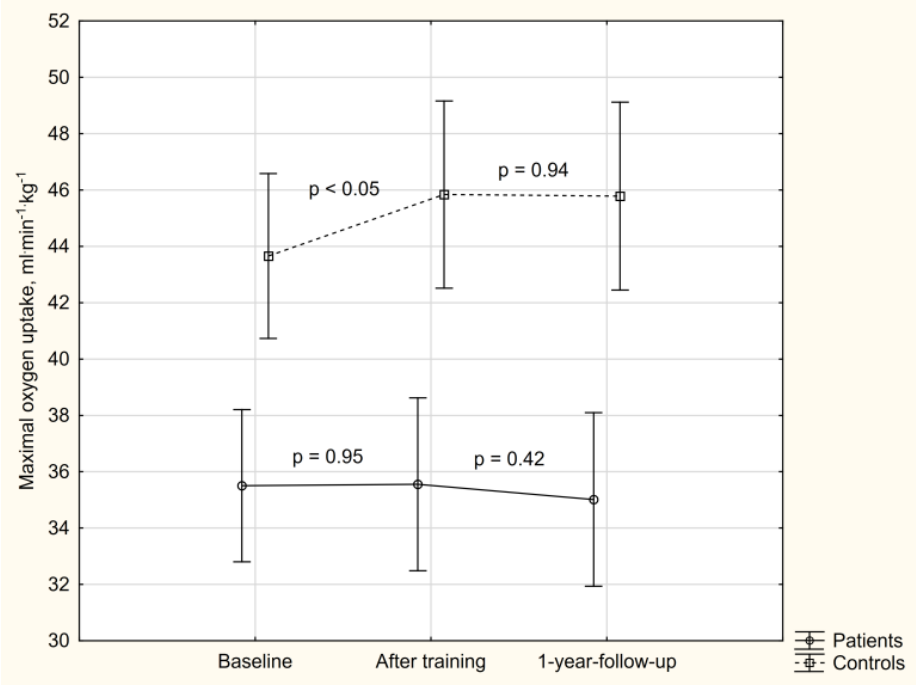

Figure 7. Maximal oxygen uptake at baseline, after training, and at follow-up after one year for patients and controls. Reused with permission from publisher.

Patients did not increase maximal elimination of carbon dioxide, $\dot{V}CO_{2max}$, after the exercise intervention, as the controls did ($p < 0.05$). Maximal minute ventilation, $\dot{V}E_{max}$, stayed

unchanged for both groups troughout the study period. VE/VCO_2 at maximal exhaustion stayed unchanged for both groups after the exercise intervention. After one year, however, VE/VCO_2 increased for patients ($p < 0.05$), while the controls had similar values as after the intervention ($p = 0.63$) (Table 6).

Oxygen pulse increased significantly after training for controls (from 11.0 ± 3.6 to 12.0 ± 4.2 $ml \cdot beat^{-1}$, $p < 0.05$) and remained at the higher level at follow-up after one year. Our patients, however, did not change oxygen pulse during the study period.

Quality of life

Patients improved their quality of life after the exercise intervention ($p < 0.01$) when analysed with the PedsQL instrument. The improvement in the patients' quality of life was both in the physical domain ($p < 0.01$) and the psychosocial domain ($p < 0.05$) of the instrument. After one year, the improved PedsQL score after training for the patients was sustained at a higher level. The controls did not report a change in quality of life throughout the entire study period (Table 5 and Fig 8).

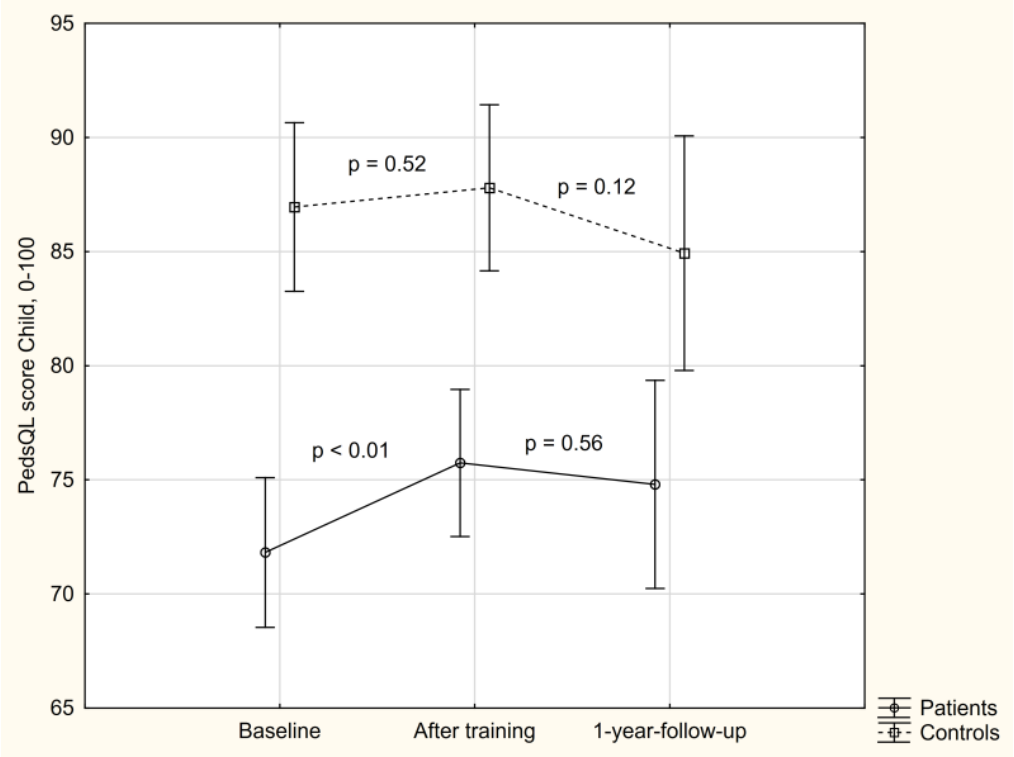

Figure 8. Quality of life scores at baseline, after training, and at follow-up after one year for patients and controls. Reused with permission from publisher.

The parental PedsQL score also increased after the exercise intervention for patients ($p < 0.001$), in both the physical and psychosocial domains. This improvement was still present after one year. The parental PedsQL score for the controls stayed unchanged throughout the study period (Table 5).

Positive predictors of quality of life were not having a heart defect ($p < 0.001$) and walking a longer distance in a 6-minute walk test ($p < 0.05$) in a multiple stepwise regression model.

5.3 PAPER III

The objective of Paper III was to study lung function in children with Fontan circulation compared with healthy children and to see if endurance training could improve lung function.

Patients had a tendency to decreased forced vital capacity (FVC), forced expiratory volume in one second (FEV1.0), and vital capacity (VC) in absolute values, while % of predicted values were significantly decreased for FVC and VC compared with the controls. The two groups had similar values regarding total lung capacity (TLC), functional residual capacity in plethysmograph (FRCPL) and measured with nitrogen wash-out (FRCN2), residual volume (RV), and lung clearance index (LCI). Patients showed signs of trapped gas, with increased portion of RV to TLC compared with the controls (26 ± 6 % vs. 22 ± 5 %, $p < 0.05$). Moreover, patients had a decreased pulmonary diffusing capacity (DLCO) compared with controls (4.27 ± 1.16 mmol·kPa^{-1}·min^{-1} vs. 6.61 ± 1.88 mmol·kPa^{-1}·min^{-1}, $p < 0.001$) (Table 7). Diffusing capacity increased with age in both groups, but significantly less in patients than controls ($p < 0.05$) (Fig 9).

Table 7. Results from lung function tests at baseline

	Patients	Controls	p	Valid N patients	Valid N controls
Dynamic spirometry					
FVC, liter	2.68 ± 0.94	3.20 ± 1.02	0.055	30	25
FVC, % Ref	86 ± 17	97 ± 13	0.010	30	25
FEV1.0, liter	2.35 ± 0.68	2.79 ± 0.96	0.054	30	25
FEV1.0, % Ref	84 ± 13	90 ± 12	0.052	30	25
FEV1.0/FVC, %	90 ± 7	87 ± 7	0.154	30	25
FEF50%, l/sec	3.60 ± 0.92	3.93 ± 1.58	0.339	30	25
FEF50%, % Ref	99 ± 20	97 ± 24	0.693	30	25
FEF75%, l/sec	1.83 ± 0.58	1.99 ± 1.03	0.482	30	25
FEF75%, % Ref	97 ± 27	91 ± 32	0.497	30	25
Static spirometry					
VC, liter	2.80 ± 0.97	3.37 ± 1.12	0.051	29	25
VC, % Ref	87 ± 15	97 ± 11	0.006	29	25
TLC, liter	3.81 ± 1.24	4.41 ± 1.65	0.142	27	25
TLC, % Ref	99 ± 15	104 ± 11	0.176	27	25
FRCPL, liter	1.84 ± 0.70	1.97 ± 0.68	0.522	27	25
FRCPL, % Ref	111 ± 23	106 ± 21	0.482	27	25
FRCN2, liter	1.78 ± 0.59	2.01 ± 0.72	0.193	29	25
FRCN2, % Ref	102 ± 19	109 ± 22	0.249	29	25
RV, liter	1.06 ± 0.44	1.10 ± 0.59	0.785	27	25
RV, % Ref	167 ± 57	151 ± 55	0.315	27	25
Pulmonary diffusing capacity					
DLCO, mmol·kPa-1·min-1	4.27 ± 1.16	6.61 ± 1.88	< 0.001	29	25
DLCO, % Ref	60 ± 11	87 ± 10	< 0.001	29	25
LCI	5.93 ± 0.95	5.72 ± 0.59	0.339	30	25

Values are presented as Mean ± 1SD
FVC = Forced vital capacity
FEV1.0 = Forced expiratory volume at the end of the first second
FEF50% = Forced expiratory flow at 50% of FVC exhaled
FEF75% = Forced expiratory flow at 75% of FVC exhaled
VC = Vital capacity
TLC = Total lung capacity
FRCPL = Functional residual capacity, plethysmography
FRCN2 = Functional residual capacity, N2 wash-out
RV = Residual volume
DLCO = Diffusing capacity for carbon monoxide
LCI = Lung clearance index
% Ref = Percentage of normal reference values (see Methods)

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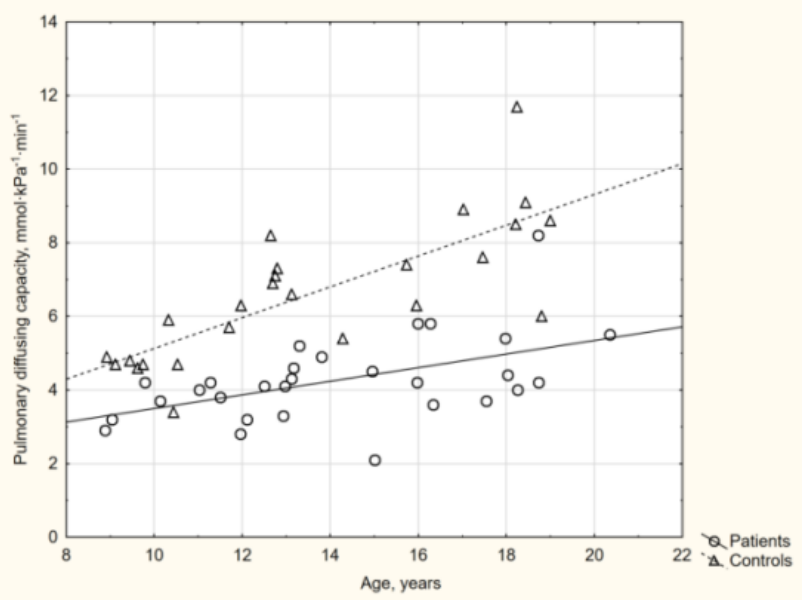

Figure 9. Pulmonary diffusing capacity vs. age in patients and controls. Reused with permission from publisher.

Effects of endurance training program

Patients improved their vital capacity after the exercise intervention ($p < 0.05$), but the controls did not ($p = 0.22$). After one year, vital capacity had increased significantly for both groups (Table 8) (Fig 10).

Table 8. Results after endurance training and at 1-year follow-up

	1. BASELINE			2. AFTER TRAINING 12 WEEKS			3. 1 YEAR FOLLOW-UP		
	Patients	Controls	p	Patients	Controls	p	Patients	Controls	p
Number, N	30	25		29	25		28	23	
Female/male, N	14/16	12/13	0.92	13/16	12/13	0.82	12/16	11/12	0.72
Age (years)	14.2 ± 3.2	13.6 ± 3.5	0.50	14.5 ± 3.2	13.9 ± 3.5	0.53	15.1 ± 3.2	14.6 ± 3.4	0.60
Weight (kg)	43.9 ± 11.8	49.1 ± 16.0	0.17	45.4 ± 12.1	50.7 ± 16.0	0.17	47.6 ± 12.4	51.9 ± 14.5	0.26
Height (m)	1.53 ± 0.14	1.58 ± 0.16	0.29	1.54 ± 0.14	1.59 ± 0.16	0.26	1.57 ± 0.14	1.62 ± 0.15	0.29
FVC (Liter)	2.68 ± 0.94	3.20 ± 1.02	0.06	2.74 ± 0.90	3.26 ± 0.98	0.05	2.94 ± 0.89	3.37 ± 0.92	0.10
FEV1.0 (Liter)	2.35 ± 0.68	2.79 ± 0.96	0.05	2.38 ± 0.68	2.79 ± 0.91	0.07	2.56 ± 0.70	2.90 ± 0.86	0.13
VC (Liter)	2.80 ± 0.97	3.37 ± 1.12	0.05	2.91 ± 0.95	3.43 ± 1.06	0.07	3.08 ± 0.95	3.56 ± 0.98	0.08
DLCO (mmol·kPa-1·min-1)	4.27 ± 1.16	6.61 ± 1.88	<0.001	4.33 ± 1.37	6.35 ± 1.89	<0.001	4.64 ± 1.49	6.89 ± 1.96	<0.001
LCI	5.93 ± 0.95	5.72 ± 0.59	0.34	5.84 ± 0.83	5.70 ± 0.58	0.50	5.87 ± 1.03	5.90 ± 0.51	0.92

Values presented as Mean ± 1SD

FVC = Forced vital capacity

FEV1.0 = Forced expiratory volume at the end of the first second

VC = Vital capacity

DLCO = Diffusing capacity for carbon monoxide

LCI = Lung clearance index

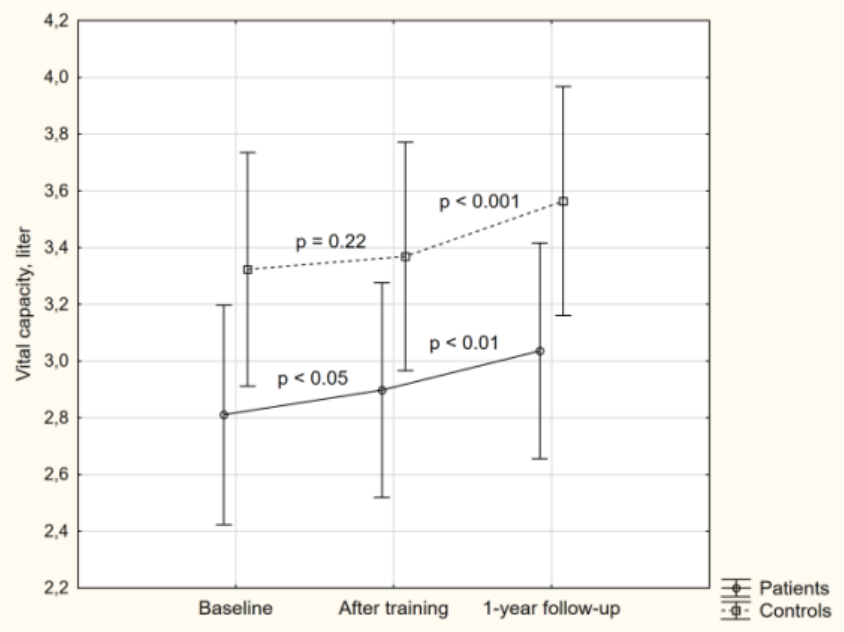

Figure 10. Vital capacity at baseline, after training, and at follow-up after one year for patients and controls. Reused with permission from publisher.

No other lung variables changed after the exercise intervention for patients or controls. After one year, FVC and FEV1.0 had increased significantly for both groups. Also, after one year, patients had similar diffusing capacity as after the interventions ($p = 0.18$), while the controls had an increased diffusing capacity compared with after the intervention ($p < 0.01$) (Table 8).

We found a correlation between pulmonary diffusing capacity and maximal oxygen uptake (Fig 11) for all participants. Positive predictors of maximal oxygen uptake were pulmonary diffusing capacity ($p < 0.001$) and weight ($p < 0.001$).

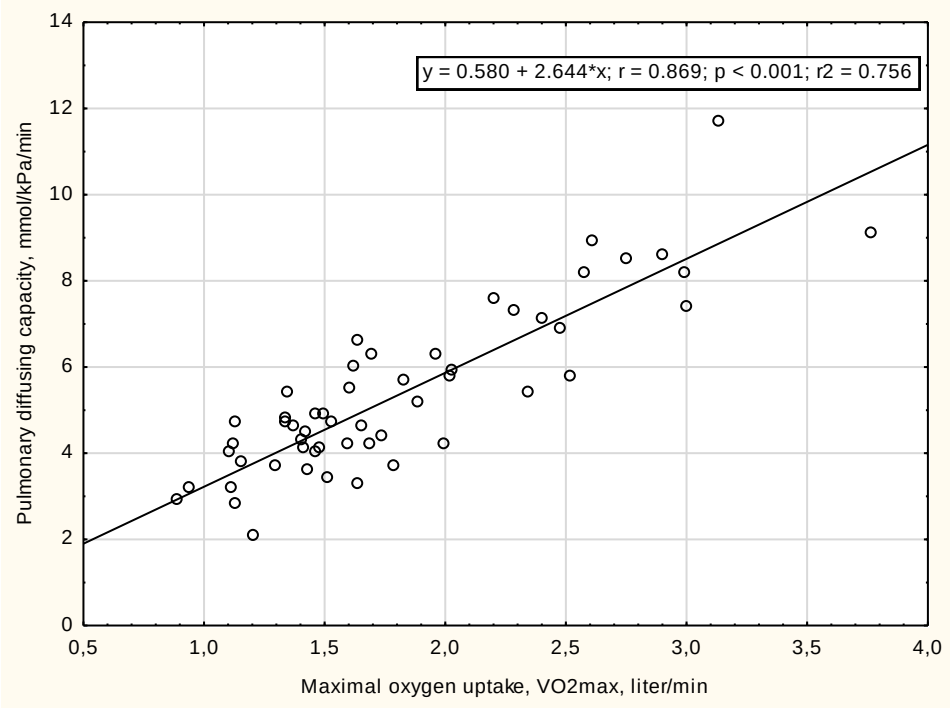

Figure 11. Pulmonary diffusing capacity vs. maximal oxygen uptake for all study subjects.

5.4 PAPER IV

The objective of Paper IV was to study sleep and if endurance training could improve sleep and sleep quality in children after Fontan palliation.

In Paper IV, the number of patients (n = 27) and controls (n = 22) included in analyses were all participants with three accepted recordings with corresponding available sleep diaries. The groups were comparable regarding characteristics at the three visits. The groups also had similar numbers of nights analysed at baseline, after training and at follow-up after one year. As described in Paper I, patients and controls had similar objectively measured activity. Both groups increased their self-reported activity after the training period, but the objectively measured activity was similar after training for both groups.

Data for total minutes in bed before training were similar for patients and controls (543.9 (424.1–636.4) minutes vs 559.8 (455.1–643.1) minutes, p = 0.71). Latency to sleep onset in minutes was significantly longer for patients than controls (22.4 (4.3–55.3) minutes vs. 14.8 (8.6–29.4) minutes, p < 0.01). Other variables like total sleep time, sleep efficiency, total counts during sleep time, number of awakenings, length of average awakening, and wake

after sleep onset were similar between the groups (Table 9). No gender differences were found in sleep variables, in either the patient group or the control group. Total sleep time decreased with age in both patients ($p < 0.001$) and controls ($p < 0.001$). Sleep efficiency showed a tendency to decrease with age in patients ($p = 0.05$), but not in controls ($p = 0.81$).

Table 9. Results sleep analyses

	Patients N = 27	Controls N = 22	p
Total minutes in bed (min)	543.9 (424.1 - 636.4)	559.8 (455.1 - 643.1)	0.710
Total sleep time (min)	437.1 (305.4 - 511.7)	432.7 (341.8 - 504.2)	0.880
Sleep efficiency (%)	79.4 (63.0 - 87.8)	78.4 (68.6 - 87.3)	0.740
Total counts night	60050 (32089 - 131082)	55337 (25865 - 122276)	0.817
Latency (min)	22.4 (4.3 - 55.3)	14.8 (8.6 - 29.4)	0.008
Awakenings (N)	25.4 (15.2 - 34.2)	28.1 (13.4 - 35.8)	0.191
Average awakening (min)	3.7 (2.3 - 7.1)	3.7 (2.7 - 9.6)	0.952
WASO (min)	91.4 (49.4 - 163.3)	95.1 (50.9 - 167.7)	0.527

Values are presented as median (min - max)

Values are mean values from three separate recordings

WASO = Wake after sleep onset

Data regarding physical activity in the daytime showed that time in moderate-to-vigorous physical activity was positively correlated with increased total sleep time ($p < 0.05$), improved sleep efficiency ($p < 0.01$) (Fig 12), and less time as wake after sleep onset during the sleep period ($p < 0.05$) for patients, but not for controls.

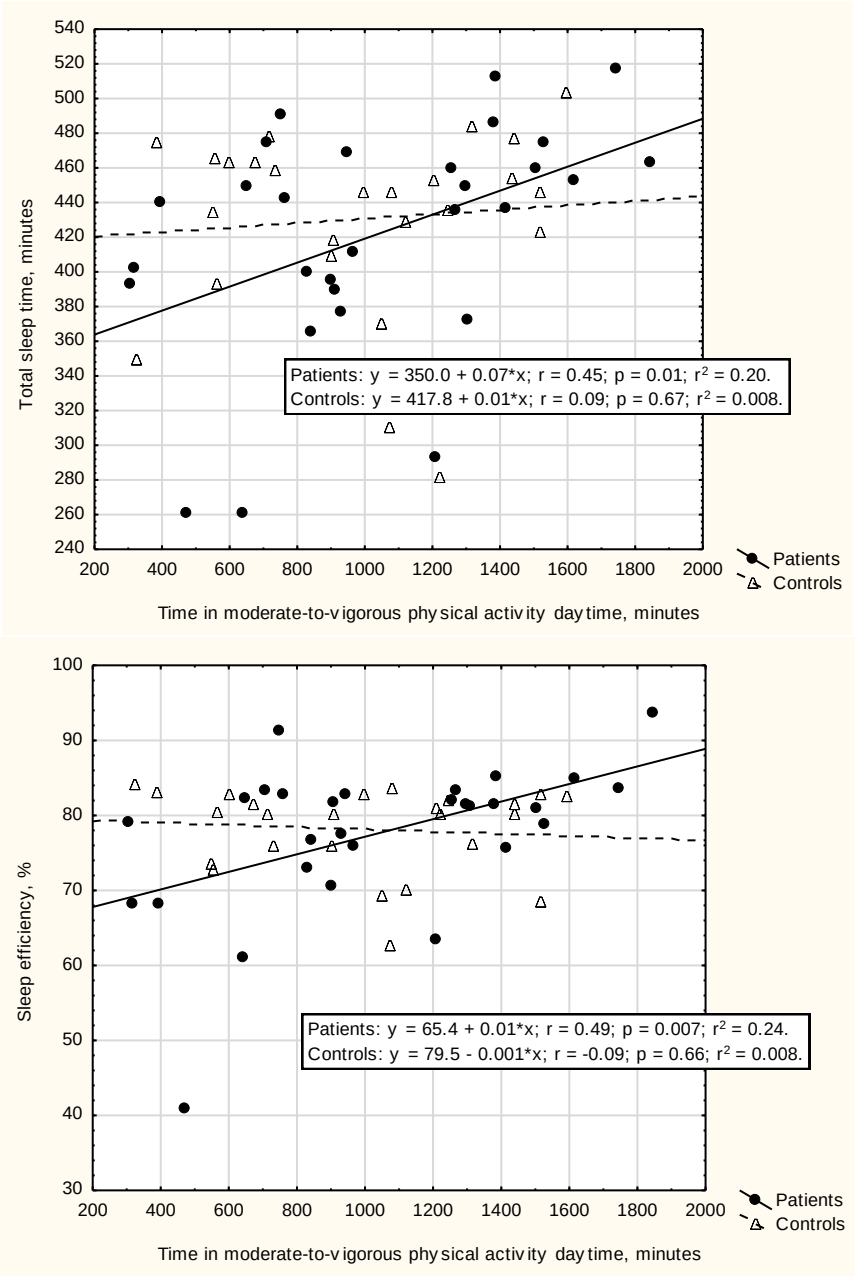

Figure 12. Total sleep time in minutes and sleep efficiency (%) vs. time in moderate to vigorous physical activity daytime in minutes for patients and controls.

Effects of endurance training program

Patients and controls did not change their total sleep time, sleep efficiency, total accelerometer counts during sleep time or amount of time as wake after sleep onset after the training programme. However, patients with low sleep efficiency at baseline increased their sleep efficiency significantly ($p < 0.05$) after the training programme, while patients with higher sleep efficiency at baseline did not.

At follow-up after one year, patients had a decreased total sleep time, decreased sleep efficiency, increased total accelerometer counts during sleep time, and increased time as wake after sleep onset. These sleep variables were unchanged for the controls at follow-up after one year. Total minutes in bed and latency to sleep onset did not change during the whole study for patients or controls.

In a multiple stepwise regression model for participants, positive predictors of sleep efficiency were female gender ($p < 0.05$) and time in moderate-to-vigorous physical activity ($p < 0.01$). The correlation between sleep efficiency and time in moderate-to-vigorous physical activity was seen in the patient group only.

6 DISCUSSION

The aim of this thesis was to evaluate if physical exercise could improve cardiopulmonary function and also quality of life in patients with Fontan circulation. Measurements of physical activity, physical capacity, lung function, quality of life, and sleep were done and retested after an individualised endurance training programme in children with Fontan circulation and a healthy matched control group. Furthermore, a 1-year follow-up was performed in order to study long-term effects. To this day, there is little knowledge regarding impact of physical exercise on quality of life in this group of patients compared with healthy children. Since studies have reported a decline over time in physical activity and performance in the general paediatric population (92, 93), we considered it important to perform a simultaneous case and control group study.

6.1 PHYSICAL ACTIVITY AND QUALITY OF LIFE (I)

Paper I showed that patients with Fontan circulation reported less time in physical exercise than healthy controls. However, the overall objectively measured activity and the amount of time in moderate-to-vigorous activity did not differ between the patients and controls. The patients reported a lower quality of life than the controls.

There was no difference between patients and controls regarding total vector magnitude, even though the patients had significantly shorter time spent in self-reported physical exercise by patients. This could be explained by the significantly shorter time in sedentary activity and longer time in light activity among the patients. Our results are in agreement with those of McCrindle et al. (23), who did not find a relationship between objectively measured and self-reported physical activity. This may reflect a different physical behaviour, day and night, in patients with Fontan circulation compared with healthy children. These patients may spend less time in sedentary activities and less time in highly intense organised physical exercise. Also, there may be fewer sports offered in the society that are suited for children with special needs. The patients may compensate with more light forms of activity outside of organised exercise. Also, if these patients may choose to interact with peers who are less physically active than other healthy children, they may engage less in organised exercise. It was shown by Longmuir et al. (94) that factors associated with physical activity were primarily unrelated to cardiac status, for example time of year, amount of outdoor time, family income, and the child's confidence in their own ability. These aspects may support our results that patients with Fontan circulation reported less time in organised exercise, but had the same amount of objectively measured activity with accelerometers.

The lower PedsQL scores among the patients were seen in both the physical and psychosocial domains of the PedsQL instrument. Furthermore, the parents' PedsQL scores were lower for patients than controls. This has also been shown in other studies (40, 43). In contrast, Hock et al. (24) showed that children with Fontan circulation had similar health-related quality of life as healthy children even though they had impaired motor function and exercise capacity. However, the healthy controls in that study were not individually matched to the patients, although they were from the same geographical area. The lower PedsQL scores in our study, with a matched control group, may support the notion that Fontan patients should be encouraged to be more physically active, in order to achieve a higher quality of life (39). However, it cannot be excluded that a lower quality of life can result in less physical activity. Interventions with exercise programmes have been studied in Fontan patients and these have resulted in improved health-related quality of life, as shown by Dulfer et al. (52). Nonetheless, more research is needed to better understand functional capacity and its relation to quality of life in this patient group.

The healthy peers of the patients reported less time in physical exercise, had less objectively measured activity, and a lower quality of life than the controls recruited by the research team. These observations suggest that Fontan patients tend to choose peers with lower quality of life and performing less physical activity than other healthy children. However, the self-selection of controls permitted comparisons between matched groups from the same contexts and maybe with similar interests in physical activities.

To summarise, our results from Paper I suggest that Fontan patients spend less time in organised physical activities and have a lower quality of life than healthy children. The objectively measured activity was, however, similar between patients and controls.

6.2 PHYSICAL CAPACITY, QUALITY OF LIFE AND EFFECTS OF EXERCISE (II)

Paper II showed that our patient group had a decreased physical capacity compared with healthy controls. Patients increased their submaximal exercise capacity and their quality of life after the exercise intervention. Patients did, however, not increase their maximal exercise capacity after the intervention. After one year, the patients had increased their submaximal exercise capacity even more and the quality of life was still increased as after the intervention. The controls increased their maximal exercise capacity after the exercise intervention. After one year, maximal exercise capacity was still increased as after the

intervention for the controls. The controls had unchanged submaximal exercise capacity and quality of life throughout the study period.

Even though the patients increased amount of self-reported exercise with a higher intensity during the exercise intervention, they did not increased their maximal exercise capacity. This has also been reported by other researchers who may have had too short duration of the intervention (95) or too low intensity of the exercises (50). Duppen et al. (96) also studied the effect of exercise training and did not show an improvement in maximal oxygen uptake in patients with Fontan circulation. They discussed that a possible explanation for this was that a relatively high maximal oxygen uptake at baseline in their patients, similar to that of our patient group (35.0 ± 5.1 ml/min/kg at baseline), might not allow for an increase after an exercise intervention.

Sutherland et al. (46) have reviewed studies on effects of exercise in patients with Fontan circulation and they recommend interventions to have twice weekly sessions during two months at least. In line with this, our exercise interventions were constructed with twice weekly sessions for three months. O'Byrne et al. (97) speculated if patients with Fontan circulations engage in exercises at a lower intensity due to exercise restrictions and that this could affect their ability to increase maximal exercise capacity. Our patients had a lower intensity of activities at baseline than controls, but did increase the intensity of activities after the exercise intervention. The individual programmes were constructed together with the child and parent/s. We considered it important to individualise the exercise interventions since the subjects had different interests and experiences of physical exercise at baseline, hoping that the children would enjoy and continue exercising after the intervention. We did not find a correlation between maximal exercise capacity and quality of life, in line with the study by O'Byrne et al. (97). Our results suggest that submaximal exercise capacity is more important for quality of life and, thus, well-being, rather than maximal exercise capacity. More studies would be useful on impact of and responses to exercise in patients with Fontan circulation compared with the impact and response in healthy children.

Our training programmes consisted of endurance aerobic training. Traditionally, aerobic training has been the standard recommendation for exercise in children with congenital heart disease, rather than muscle strength training. There is not much knowledge about the effects of muscle strength training in children with Fontan circulation. Studies (98-100) have shown that adults with complex congenital heart diseases have impaired skeletal muscle function. Cordina et al. (98) showed, on a small number of adult Fontan patients, that isolated muscle training was safe and might increase cardiac filling, cardiac output, and also exercise

capacity. Cordina et al. (98) also showed that reduced muscle mass was correlated with reduced exercise performance and oxygen pulse (a surrogate for stroke volume). They speculated whether greater muscle mass could increase exercise capacity through an strengthened peripheral muscle pump. Association between the skeletal muscle pump and cardiac output in Fontan patients has been shown by Shafer et al. (101). More research is needed on muscle resistance training and its effect on children with Fontan circulation.

Patients with Fontan circulation have a reduced ability to increase stroke volume and cardiac output during exercise (12). A valid estimate of stroke volume is oxygen pulse (oxygen uptake, VO_2, divided by heart rate) and this has been shown in healthy adolescents (91). Healthy non-athlete adolescents have been shown to have an oxygen pulse of 13.2 ± 2.5 $ml \cdot beat^{-1}$ for males and 11.0 ± 1.7 $ml \cdot beat^{-1}$ for females (91). We found that the oxygen pulse at maximal effort was significantly smaller in our patients than in controls (9.7 ± 2.9 vs. 11.7 ± 3.8 $ml \cdot beat^{-1}$, $p < 0.05$). Oxygen pulse increased after training for controls and remained at a higher level at follow-up after one year. However, our patients did not have changes in oxygen pulse during the study period. These results support that these patients have a reduced cardiac output during exercise and that they have a reduced ability to increase it after an exercise intervention.

The patients increased their submaximal exercise capacity, measured with increased distance walked in a six-minute walk-test, after the exercise intervention. Banks et al. (68) have suggested that these patients have a more efficient peripheral oxygen extraction by the skeletal muscles, as a result of decreased oxygen saturation early in life. They propose that these patients may tolerate exercise at submaximal level better than at maximal levels. Patients had unchanged maximal heart rate after the walk-test, when comparing before and after the exercise intervention; this indicates increased peripheral effectiveness rather than central in response to exercise. Wittekind et al. (102) also reported increased maximal and submaximal exercise capacity in patients with Fontan circulation after exercise training, partly explained by more efficient oxygen utilization rather than central mechanisms.

Our results showed a significant improvement of walking distance in the patient group of 4% and an absolute value of 21 meters. This is within range of the minimal clinically important difference from the review values from Schrover et al. (71), but it is difficult to draw conclusions from comparisons with other chronic diseases. When comparing with the control group in our study, the controls did not walk a significant longer distance after training period, which the patients did. Also, there was a corresponding improvement in quality of life in the patient group after training and 6MWT distance was a positive predictor of quality of

life. This strengthens the implication and importance of physical exercise and its beneficial effects on quality of life in patients with Fontan circulation.

Both groups increased exercise in minutes per week after the exercise intervention. After one year, however, patients decreased amount of exercise down to baseline levels. Patients had a lower intensity of the activities compared with the controls at baseline, as mentioned earlier. However, after the exercise intervention and after one year, the average intensity of activities did not differ between the two groups any longer. Patients might have participated in activities and daily life with increased intensity after the intervention. This can be the explanation for the improved submaximal capacity and preserved quality of life after one year. This may be important for these patients in their daily life.

During maximal exercise testing, the patients reacted with a limited ability to increase heart rate and blood pressure, and decreasing oxygen saturation compared with the controls. These patients' limited ability to increase preload and, thus also, cardiac output during exercise would be the explanation for this and the reduced maximal performance. They may also lack experience or motivation, or fear of complications or severe symptoms, in order to perform activities at higher intensities. However, the limitation in maximal heart rate response in this patient group may not influence submaximal exercise capacity (68).

Other factors that may reduce exercise capacity are abnormal lung function and gas exchange, which has been shown in patients with Fontan circulation (32). Idorn et al. (33) have reported a reduced diffusing capacity and an association with a reduced capillary blood volume in the lungs. The decreased oxygen saturation that was seen during maximal exercise testing can also be explained by possible intrapulmonary shunting. This might limit alveolar diffusion of gas. VE/VCO_2, as a measure of ventilatory efficiency, was impaired in the patient group, as has also been shown by Hock et al. (24). In addition, during cardiopulmonary exercise testing, VE/VCO_2 had increased after one year only for patients, and not for controls. This worsening ventilator efficiency over time is of course concerning, but effects on the patients are unclear and more research is needed (90). The decreasing ventilatory efficiency and abnormal diffusing capacity in response to growth may reflect abnormal pulmonary vascular growth and/or gas exchange properties. One may also speculate whether this could be secondary to abnormal pulmonary blood flow early in life or a secondary effect of the non-pulsatile pulmonary hypoperfusion in the Fontan circulation. Efforts and interventions to maintain or even improve ventilation and lung function in these patients are needed.

Quality of life was improved after the exercise intervention, when reported by the patients and their parents. The healthy children and their parents reported unchanged quality of life after the intervention. Thus, an individualised exercise intervention may improve quality of life in patients with Fontan circulation and the effect may be long-lasting. This change is maybe not expected in a healthy group of children with a high self-reported quality of life at inclusion of the study. The higher PedsQL score for the patients is greater than the minimal clinically important difference for the PedsQL instrument as described under 'Methods', indicating an important actual clinical effect for these patients.

Jacobsen et al. (53) studied effects of a home-based 12-week exercise programme in 14 patients with Fontan circulation and found improved exercise capacity and that parents, but not the patients themselves, reported an improved health-related quality of life. Their exercise programmes were identical for all subjects and included dynamic and static exercises presented on a DVD or paper handout. Our exercise programmes were individually based on the child's performance and own interests, as described earlier. In order to achieve compliance, a higher quality of life, and enjoyment of activities and exercises, it might be important that the children themselves can choose and participate in sports and activities that they like. Health-related quality of life is, however, likely multifactorial and more research is needed to better understand effects and risk factors for impaired quality of life.

Exercise training can improve quality of life and, thus, also daily life of patients with Fontan circulation. We believe that these patients should be encouraged to be physically active and that rehabilitation programmes should be developed and included in the medical care of these patients.

6.3 LUNG FUNCTION AND EFFECTS OF EXERCISE (III)

Paper III showed that children who have undergone Fontan palliation have impaired lung function and a tendency of restrictive lung physiology. Pulmonary diffusing capacity was reduced and these patients also have signs of air trapping compared with healthy controls. Vital capacity increased after an exercise intervention for the patients. This was not seen for the controls. Moreover, diffusing capacity increased with age and growth for both patients and controls, but significantly less in the patient group. This suggests an abnormal lung development with growth in the patients and/or a worsening pulmonary vasculopathy.

Turquetto et al. (103) have also reported restrictive lung physiology, reduced diffusing capacity, and an association between lung function and exercise capacity in these patients. A multi-center study by Opotowsky et al. (32) also showed the association between impaired lung function and exercise capacity. They proposed that surgical interventions might affect the chest wall and, thus, results in a reduced lung function and impaired lung development.

Matthews et al. (35) also studied lung function in these patients and speculated that a reduced diffusing capacity might be a result of the non-pulsatile pulmonary circulation, with a constant flow and pressure in the vasculature. This might affect the alveolar capillary membranes negatively and resulting in decreased diffusing capacity. Idorn et al. (33) reported that diffusing capacity, in patients with Fontan circulation, increased when patients were lying down, horisontally. In the horisontal position, they report that pulmonary capillary blood volume increases for patients with a non-pulsatile flow through the lungs, and this results in an increased diffusing capacity. Yin et al. (104) reported a redistribution of pulmonary blood flow in children with Fontan circulation with, for example an increased blood flow to lower lung segments compared with upper lung segments. This might be the cause of the reduced diffusing capacity. Mettauer et al. (105) presented lung function, with a restrictive lung physiology and reduced diffusing capacity, in adults with chronic heart failure. They speculated that the impaired lung function could be a result of permanent vascular changes of the pulmonary vasculature, related to duration and severity of heart failure. One can see possible similarities in reduced diffusing capacity between patients with chronic heart failure and pulmonary venous congestion and Fontan patients with systemic venous congestion.

The patients had signs of air trapping and this has also been shown in earlier studies (35, 36). This could be a result of several surgical procedures that leads to a restrictive lung physiology and non-ventilated lung sections peripherally. Ohuchi et al. (36) and Turquetto et al. (103) both suggest that the restrictive physiology and air trapping may limit exercise performance in these patients.

An increase in vital capacity was seen in the patient group but not for the controls, after the exercise intervention. Thus, physical exercise might be beneficial for lung function in patients with Fontan circulation. Developed chest musculature may contribute to the increase in vital capacity in these patients, but more research is needed to clarify this. Regarding respiratory muscle training, Laohachai et al. (106) have demonstrated that it can increase muscle strength, result in more effective ventilation during exercise, and also increase resting cardiac output in Fontan patients. They proposed that physical exercise may improve exercise

performance and, in the long run, reduce morbidity and mortality. Ait Ali et al. (107) also showed that controlled respiratory training might improve cardiopulmonary performance during exercise in these patients. These studies support our results and speculations that physical exercise may improve chest musculature and vital capacity in our patient group. However, the clinical importance of the small but significant increase in vital capacity in the patient group is unclear. Quality of life was improved after this exercise intervention as well, as mentioned earlier, but it is difficult to argue which measured improvement of cardiopulmonary function, or other factor, that is the main factor contributing to an improved quality of life.

Our results also suggest that maximal oxygen uptake is dependent on diffusing capacity (Fig 11). This association has been presented before, in healthy subjects with different exercise capacities, by Zavorsky et al. (108). They reported that subjects with a high exercise capacity also had a high diffusing capacity and those with a lower exercise capacity, also had a lower diffusing capacity. Thus, Fontan patients' reduced diffusing capacity may affect their maximal oxygen uptake and exercise capacity. Early palliative surgical procedures, to optimise pulmonary blood flow, can support lung growth and prevent permanent lung damage. Impaired lung function might affect physical performance and, thus, daily life during childhood and into adult life.

Thus, children with Fontan circulation should engage in physical activities and sports in order to improve exercise capacity as well as lung function, and ultimately improve their quality of life.

6.4 SLEEP AND EFFECTS OF EXERCISE (IV)

A clinical problem, raised by the patients and their parents, is sleep disturbances of various types. Paper IV is the first study that analyses sleep in patients with Fontan circulation compared with healthy control subjects before and after an endurance training programme and after one year. Our results showed that patients with Fontan circulation have sleep duration and sleep efficiency similar to healthy children. The patients, however, had a prolonged latency to sleep onset compared with healthy control subjects. Also, we found that increased time in moderate-to-vigorous physical activity during daytime was positively correlated with increased sleep efficiency in the patient group, but not in the control group.

Patients and controls met the recommended hours of sleep duration in both younger and older subjects (109). Moreover, our results showed a tendency for increasing age being associated

with decreased sleep efficiency in patients, but not in controls. Increased time in moderate-to-vigorous physical activity during daytime was positively correlated with increased sleep efficiency in the patient group, but not in the control group, as mentioned earlier. Lang et al. (110) studied healthy adolescents and also showed that higher levels of physical activity were related to better subjective and objective sleep and sleep quality. In addition, Stone et al. (111) showed a positive relationship between physical activity and sleep duration in healthy children. Adolescents sleep shorter time and are less active than younger children, thus a model must adjust for age to avoid misleading results. As our patients and controls were matched for age and gender, we believe this risk was low in our study. More research is needed to better understand the mechanisms and relationship between amount of physical activity in daytime and sleep in patients with Fontan circulation.

After endurance training, neither sleep duration nor sleep efficiency changed for patients or controls. Patients and controls with low sleep efficiency at baseline did, however, increase their sleep efficiency significantly more ($p < 0.05$) after the training programme than subjects with high sleep efficiency at baseline. Thus, it seems that subjects with low sleep efficiency benefits more from endurance training than subjects with higher sleep efficiency. Kredlow et al. (112) reviewed studies of effects of physical activity on sleep in adults and showed acute benefits of exercise on many sleep parameters, and also greater subjective and objective sleep benefits of regular exercise over longer time. Our training programmes may have been of suboptimal duration and/or intensity for maximal positive effects for our patients and more research is needed to understand the effects of exercise on sleep in this patient group compared with healthy children.

Our patients and their parents reported a long recovery time after physical activity and fatigue the day after physical exercise. This is important to take into consideration and individually designed physical activities in schools and in the community should be available for children with complex congenital heart malformations to perhaps minimise these side effects. This is not offered in society today.

At follow-up after one year, patients had decreased their total sleep time and sleep efficiency. These changes were not seen in the control group. Thus, patients and controls differed at follow-up after one year, which is concerning. Even though objectively measured activity did not change for patients or controls after training or at follow-up after one year, self-reported exercise decreased for patients, but not controls, at follow-up after one year. This could explain a worsening sleep pattern in the patient group over time. However, one cannot rule

out that worsening sleep patterns may have a negative impact on a child's ability to engage in exercise and sports.

To summarise, patients with Fontan circulation seem to have a prolonged latency to sleep onset compared with healthy children. Also, more time spent in physical activities of higher intensities seems to be beneficial for sleep quality in children with Fontan circulation. More research is needed to better understand the impact of and optimal regimens for exercise with regard to sleep and sleep quality in this patient group.

6.5 CONTRAINDICATIONS / RISKS WITH EXERCISE

There are, today, no absolute restrictions on physical activity for children and adults with congenital heart malformations. However, physical activity is not recommended if patients have acute illnesses, acute heart conditions or severe symptoms during exercise. Counselling regarding physical activity should always be individualised, since this is a heterogeneous group of patients with varying physical performances and risk factors. Patients with malignant arrhythmias and severely decreased systolic ventricular function, for example, are recommended to perform physical activities at lower intensities. Medications are common in this patient group. Betablockers can limit heart rate at rest and exercise. Anticoagulation can be a risk with sports that include body contact and individual counselling should be provided. Other heart medications are usually not regarded as added risks during exercise.

The effects of physical exercise in patients with Fontan circulation are not fully understood. A review of effects of exercise training in children with various congenital heart diseases was performed by Duppen et al. (113) and they concluded that exercise was safe and improved fitness in these patient groups. In addition, Duppen et al. (114) have demonstrated that no adverse heart effects or cardiac remodelling were seen after exercise training in patients with Fontan circulation. They recommended that children with congenital heart disease, including patients with Fontan circulation, should participate in exercise training and that it should be part of the treatment of these patients. Long-term effects of exercise training in this patient group over longer time than one year have not been studied.

6.7 STRENGTHS AND LIMITATIONS

We studied 30 patients with Fontan circulation and the number of patients was limited by the Fontan cohort in the Stockholm region as presented under 'Material'. The patients that joined

the study might represent a group of patients with better outcome than those who declined participation. We did not get ethical permission to analyse characteristics from patients who were excluded or declined participation in the study. The selection of control subjects can be argued, but we wanted to compare physical activity and quality of life in healthy children, who the patients are likely to compare themselves with. A matched control group for comparisons was considered important, in order to avoid comparisons with old reference material, since studies have shown a decline in physical activity and exercise performance in the general population over time (92, 93).

The self-selected controls by the patients spent less time in physical activities and had a lower quality of life than the controls recruited by the research team, as described in Paper I. Moreover, compared with a Swedish reference material (87), the self-selected controls by the patients had lower PedsQL scores, while the controls recruited by the research team had similar PedsQL scores as the reference material. The controls recruited from hospital staff may be a group closer to the average levels of health consciousness and physically activity than the peers selected by the patients.

Moreover, exercise interventions with other durations and/or other weekly frequencies could have resulted in other effects. The individually constructed training programmes aimed at improving compliance and, hopefully, giving greater chances for continued exercise even after one year in the study. Further studies are necessary to better understand the effects of exercise training among patients with Fontan circulation.

We compared patients and a healthy control group before and after an exercise intervention and at follow-up after one year. More information on the impact of an exercise intervention could have been given if we had included a third study group, with patients who did only the three examinations at the same intervals, but without an exercise intervention. We felt, however, that it was important to include all patients in an intervention group because of the limited size of our Fontan cohort.

Familiarisation with exercise and lung function testing is an important consideration when repeating tests. In our study, patients and controls performed identical examinations at the same intervals, enabling for comparisons to be made between the groups.

Sleep among patients with Fontan circulation is a new field of research. Paper IV enlightens sleep patterns and impact of physical activity on sleep in this patient group. Exercise interventions with other duration, frequency, and/or intensity could have altered the results,

thus, more research is needed to find optimal regimens regarding exercise and its effect on sleep.

Statistical analyses regarding gender differences and differences depending on anatomical ventricle have not been done to a larger extent because of the relative small patient number. More research is needed to clarify these aspects.

7 CONCLUSIONS

This thesis summarises our studies about effects of exercise training on cardiopulmonary function, sleep, and most importantly quality of life in patients with Fontan circulation compared with healthy controls.

Children and adolescents with Fontan circulation reported less time in regular physical exercise than healthy controls, even though the objectively measured activity levels were similar between the groups. The patients and their parents also had a lower quality of life than the controls. Moreover, children with Fontan circulation have impaired physical performance and impaired lung function. Pulmonary diffusing capacity was reduced and the normal increase of diffusing capacity with age, seen in the healthy children, was not seen in the patients. Patients with Fontan circulation seem to have a prolonged latency to sleep onset compared with healthy children. Increased time in physical activities daytime seems to be correlated with better sleep quality in patients with Fontan circulation. Endurance training improved submaximal exercise capacity, pulmonary vital capacity, and quality of life but did not improve maximal exercise capacity in children with Fontan circulation. The improvement of quality of life was sustained at follow-up after one year.

Thus, endurance training and/or increased amount of physical activity may improve submaximal exercise capacity, lung function, sleep quality, and quality of life in children and adolescents with Fontan circulation and the effect on quality of life seems to be long-lasting. The clinical importance of our results is that if increased physical activity is likely to be beneficial for cardiopulmonary function, quality of life, and sleep, patients with Fontan circulation should be encouraged to engage in regular sports and activities that are individually designed. Rehabilitation programmes should include structured individualised endurance training for improved outcome in this patient group. Further research is necessary, however, to more fully understand the effects of exercise on cardiopulmonary function, sleep, and quality of life in this patient group. Also, further studies are needed on

how to individualise recommendations and find optimal regimens for exercise prescriptions for these patients. Moreover, research is needed to study long-term effects of exercise prescriptions in this patient group. The important message is, though, to encourage physical exercise and an active lifestyle in these patients for better health and well-being.

8 CLINICAL UTILITY

This thesis provides knowledge about the impact of physical activity and endurance training on cardiopulmonary function, sleep and quality of life on children and adolescents with Fontan circulation. Our results, showing that physical activity and endurance training can improve cardiopulmonary outcome, sleep efficiency, and quality of life for children and adolescents with Fontan circulation, should guide and strengthen families and care providers to encourage these children to be more physically active.

9 FUTURE PERSPECTIVES

More studies are needed to fully understand cardiopulmonary response to exercise, as well as its effects on sleep and on quality of life over a longer period of time in this patient group. We believe that exercise prescriptions should be individualised as regards type of exercise and recommended intensity through consultation with the child and his/her parents. Future studies should, however, focus on how to best individualise exercise prescriptions and how to implement exercise in rehabilitation programmes for patients with Fontan circulation for better outcome. Attempts have been made to formulate individual recommendations for adult patients with congenital heart disease, but these recommendations are based on limited clinical evidence (115). More research is needed on effects of different types of exercise training in patients with Fontan circulation and long-term benefits, as well as risks with different exercise regimens.

10 SVENSK SAMMANFATTNING

Bakgrund

Överlevnaden hos barn med kirurgiskt pallierat enkammarhjärta, s.k. Fontancirkulation, har ökat under de senaste decennierna. Idag överlever de flesta till vuxen ålder tack vare utvecklade kirurgiska tekniker och det medicinska omhändertagandet. Dessa barns fysiska prestationsförmåga och livskvalitet blir påverkade på sikt. Det saknas kunskap om effekter av fysisk träning på hjärt- och lungfunktion och livskvalitet i denna patientgrupp jämfört med friska barn.

Syfte

Syftet med denna avhandling var att studera fysisk aktivitet, fysisk kapacitet, lungfunktion, sömn och livskvalitet före och efter en träningsintervention samt efter 1 år, hos barn med kirurgiskt pallierat enkammarhjärta och en frisk ålders- och könsmatchad kontrollgrupp. Vi ville utvärdera om fysisk träning kunde förbättra hjärt- och lungfunktionen men även livskvaliteten, på kort och lång sikt i denna patientgrupp.

Metoder

Patienter med kirurgiskt pallierat enkammarhjärta (n = 30) och friska kontroller (n = 25) genomförde tester av fysisk aktivitet, submaximal och maximal prestationsförmåga, lungfunktion, sömn och livskvalitet före och efter ett individuellt anpassat träningsprogram om 12 veckor, samt efter 1 år.

Resultat

Barn med kirurgiskt pallierat enkammarhjärta rapporterade mindre tid i organiserad fysisk aktivitet och lägre livskvalitet jämfört med friska kontroller. Den objektivt uppmätta totala aktiviteten var dock lika i båda grupperna. Barn med kirurgiskt pallierat enkammarhjärta hade nedsatt fysisk prestationsförmåga, restriktivt andningsmönster och nedsatt diffusionskapacitet (gasutbyte i lungorna). Den förväntade ökningen av diffusionskapacitet med ålder skiljde sig från den normala hos patienterna. Fysisk träning förbättrade den submaximala prestationsförmågan och livskvaliteten, men inte den maximala prestationsförmåga hos hjärtbarnen. Vid uppföljningen efter 1 år hade den submaximala prestationsförmågan förbättrats ytterligare och den förbättrade livskvaliteten bestod. Fysisk träning förbättrade också vitalkapaciteten vid lungfunktionstester.

Barn med kirurgiskt pallierat enkammarhjärta hade en förlängd insomningstid jämfört med friska barn. Ökad tid i fysiska aktiviteter av högre intensitet var korrelerat med bättre sömnkvalitet hos hjärtbarnen.

Slutsatser

Individuellt anpassade träningsprogram verkar kunna förbättra submaximal prestationsförmåga, lungfunktion och livskvalitet hos barn med kirurgiskt pallierat enkammarhjärta och förbättringen av livskvalitet håller i sig på lång sikt. Ökad tid i fysiska aktiviteter med högre intensitet verkar gynnsamt för sömnkvaliteten hos dessa barn. Om ökad fysisk aktivitet och fysisk träning är gynnsamt för hjärt- och lungfunktion, sömn och livskvalitet borde dessa barn bli uppmuntrade att delta i regelbunden individuellt anpassad fysisk träning. Rehabiliteringsprogram borde innehålla tydliga rekommendationer och strukturerad anpassad träning. Fler studier behövs för att bättre kartlägga och förstå effekter av olika typer av fysisk träning på hjärt- och lungfunktion och livskvalitet i denna patientgrupp både på kort och lång sikt. Fler studier behövs också om hur man på bästa sätt kan individualisera rekommendationer för träning i denna patientgrupp. Fysisk träning och fysisk aktivitet bör dock redan nu uppmuntras hos dessa patienter för ökat välbefinnande.

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