Physical performance, physical activity, body composition and exercise training in adults with congenital heart disease

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To my amazing family Jörgen, Christian, Simon and Linn

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Abstract

Background Adults with congenital heart disease (CHD) is a growing population and related to advances in surgical and medical treatment, they now outnumber the children with corresponding lesions. Since a congenital heart lesion often results in reduced exercise capacity, this population is a potential target for physiotherapy. To what extent this reduction in exercise capacity is caused by abnormal cardiovascular anatomy and physiology or to what degree insufficient physical activity contributes is not known. To support the advancements in paediatric cardiac care, increased knowledge regarding physical performance, physical activity level, body composition and the effects of exercise training among adults with CHD is required.

Methods In a cross-sectional study skeletal- and respiratory muscle function, physical activity level and exercise self-efficacy was investigated among 85 adults with various forms of CHD and 42 control subjects. A second study was conducted to analyse height, weight and body mass index (BMI) in 538 adults with complex CHD and 1886 adults with simple CHD. Data were extracted from the Swedish registry on congenital heart disease (SWEDCON) and compared to data from a national population survey. In a third study, factors associated with self-reported quality of life (QoL) were analysed using SWEDCON data on 315 adults with congenital aortic valve disease. Finally, a randomised controlled trial was conducted to investigate the effects of interval exercise training among adults with complex CHD.

Results Adults with complex CHD showed impaired muscle function compared to both patients with simple CHD and controls. In addition, patients with complex CHD had a lower exercise self-efficacy compared to controls. Patients with CHD were equally active at moderate-to-vigorous level as the controls. However, approximately 50% of both patients and controls failed to reach the recommended physical activity level. In general patients with CHD had the same height, weight and BMI, as the general population. However, compared to the general population, men with CHD were more commonly underweight and less commonly overweight/obese. Additionally, especially male patients with complex CHD were shorter compared to the general population. Among adults with congenital aortic valve disease, a higher physical activity level was associated with better QoL. Furthermore, interval training increased exercise capacity and endurance among adults with complex CHD.

Conclusion A higher physical activity level was associated with better self-reported QoL in patients with congenital aortic valve disease which implies that QoL might be possible to improve, by adopting a physically active life-style. Adults with CHD were equally active as controls at a moderate-to-vigorous physical activity level. However, approximately half of both groups were insufficiently physically active based on current recommendations. This indicates that low physical activity, on group level, does not explain the lower exercise capacity commonly found among patients with CHD. In addition, this is consistent the finding that the majority of patients followed the same pattern regarding BMI as seen in the general population. However, impaired muscle function in combination with the shorter stature and higher prevalence of underweight found in men, especially with complex CHD, implies an altered body composition in this group. The findings of the present thesis suggests an indication for physiotherapy targeting increased physical activity level and individualized exercise training in this patient population. Moreover, regular evaluation of muscle function, exercise self-efficacy and QoL, in addition to exercise capacity, might be useful for monitoring disease development over time.

Abbreviations

ACHD; adult congenital heart disease
AR; aortic regurgitation
AS; aortic stenosis
ASD; atrial septal defect
AVD; aortic valve disease
BAV; bicuspid aortic valve
DEXA; dual energy X-ray absorptiometry scan
DORV; double outlet right ventricle
DILV; double inlet left ventricle
CoA; coarctation of the aorta
COPD; chronic obstructive pulmonary disease
CHD; congenital heart disease
CPET; cardiopulmonary exercise testing
ESE; exercise self-efficacy
ESES; exercise self-efficacy scale
GUCH; grown-up congenital heart disease
HLHS, hypoplastic left heart syndrome
HR; heart rate
HRR; heart rate reserve
ICD; implantable cardioverter defibrillator
IPAQ; International Physical Activity Questionnaire
MEMS; microelectromechanical systems
MET; metabolic equivalent
NYHA class; New York Heart Association Classification
PA; pulmonary atresia
PA; physical activity (only used in abstract)
PDA; persistent ductus arteriosus
PFO; persistent foramen ovale
PS; pulmonary stenosis
Pts; patients
RER; respiratory exchange ratio
RVOT; right ventricular outflow tract
RVOTO; right ventricular outflow tract obstruction
d-TGA; dextro-transposition of the great arteries
ccTGA; congenitally corrected transposition of the great arteries
ToF; tetralogy of Fallot
TCPC; total cavo-pulmonary connection
THR; training heart rate
VO_2; oxygen uptake
VSD; ventricular septal defect

Sammanfattning på svenska

Vuxna med medfödda hjärtfel blir allt fler tack vare de framsteg som gjorts inom medicinsk och kirurgisk behandling. Idag är antalet vuxna större än antalet barn med motsvarande diagnoser. Många patienter med medfödda hjärtfel har nedsatt arbetsförmåga (”kondition”) i jämförelse med friska. Det är dock oklart i vilken utsträckning denna nedsättning orsakas av avvikande anatomi och fysiologi eller i vilken utsträckning exempelvis brist på fysisk aktivitet bidrar. För att kunna bemöta de medicinska behoven i denna patientgrupp och förvalta de framsteg som uppnåtts inom barnhjärtsjukvården krävs ytterligare kunskap om prestationsförmåga, fysisk aktivitetsnivå, kroppskonstitution och effekterna av träning vid medfödda hjärtfel hos vuxna.

I en tvärsnittsstudie undersöktes muskelfunktion i skelett- och andningsmuskulatur, fysisk aktivitetsnivå och tilltron till att vara fysiskt aktiv hos 85 vuxna med olika medfödda hjärtfel. Resultaten jämfördes med 42 ålders- och könsmatchade kontroller. Vidare analyserades längd, vikt och kroppsmasseindex (BMI) hos 538 vuxna med komplexa medfödda hjärtfel och 1886 med hjärtfel klassade som ”enklare”. Data från det nationella registret för medfödd hjärtsjukdom (SWEDCON) analyserades och jämfördes med populationsdata data från Statistiska Centralbyrån. Fortsättningsvis analyserades data på 315 vuxna med medfödd aortaklaffsjukdom från SWEDCON med avseende på självskattad livskvalitet. I en randomiserad kontrollerad interventionsstudie undersöktes effekterna av ett intervallträningsprogram hos vuxna med komplexa medfödda hjärtfel.

Vuxna med komplexa medfödda hjärtfel hade nedsatt muskelfunktion både i jämförelse med patienter med hjärtfel klassade som ”enklare” och kontrollgrupp. Dessutom skattade patienterna med komplexa hjärtfel sin tilltro till att vara fysiskt aktiva som lägre jämfört med kontrollerna. Patienterna med medfödda hjärtfel var lika aktiva på medel- till högintensiv aktivitetsnivå som de hjärtfriska kontrollpersonerna. Dock var ungefär hälften av både patienter och kontrollgrupp otillräckligt aktiva för att uppnå de aktuella rekommendationerna om fysisk aktivitet. Analyserna av längd, vikt och BMI visade att patienter med medfödda hjärtfel i stor utsträckning följde samma mönster som i befolkningen i övrigt. Bland män fanns en större andel av undervikt och en mindre andel av övervikt/fetma. Detta gällde särskilt patienter med komplexa hjärtfel. Dessa var också kortare i jämförelse med den övriga befolkningen. Hos patienter med medfödd aortaklaffsjukdom fanns ett samband mellan högre fysisk aktivitetsnivå och

högre självskattad livskvalité. Interventionsstudien visade att intervallträning gav ökad arbetsförmåga och förbättrad uthållighet hos de som tränat i jämförelse med de som lottats till kontrollgrupp.

Sammanfattningsvis visar studierna i denna avhandling att en högre fysisk aktivitetsnivå hade samband med bättre livskvalité hos patienter med medfödd aortaklaffsjukdom, vilket antyder att livskvalitén påverkas i positiv riktning av en fysiskt aktiv livsstil. Vuxna med medfödda hjärtfel var fysiskt aktiva i samma utsträckning som kontrollgruppen på medel- till högintensiv nivå. Däremot var ungefär hälften av både patienter och kontrollgrupp otillräckligt aktiva för att uppnå rekommendationerna om fysisk aktivitet. Eftersom det inte fanns någon skillnad mot kontrollgruppen kan det betyda att den nedsatta prestationsförmågan, som ses hos många patienter med medfödda hjärtfel, inte orsakas av brist på fysisk aktivitet. Dessutom ligger detta i linje med fyndet att en större del av patienterna följde samma mönster gällande BMI som sågs i den övriga befolkningen. Hos män med medfödda hjärtfel kan nedsatt muskelfunktion i kombination med en större andel undervikt, en mindre andel av övervikt/fetma och kortare kroppslängd, tyda på förekomst av avvikande kroppssammansättning. Detta gällde framför allt de med komplexa hjärtfel. Dock är både bakomliggande orsaker och eventuell prognostisk betydelse fortfarande okänd. Sammantaget visar resultaten i denna avhandling att fysioterapi med inriktning på ökning av den fysiska aktivitetsnivån och individuellt anpassad träning kan vara indikerad hos vuxna med medfödda hjärtfel. Fortlöpande utvärdering av arbetsförmåga och regelbunden utvärdering av muskelfunktion, livkvalité och tilltron till att vara fysisk aktiv, kan vara av värde för att bättre följa utvecklingen av hjärtfelet över tid.

Original papers

This thesis is based on the following papers, referred to in the text by their Roman numerals I-V:

I. **Sandberg C,** Thilén U, Wadell K, Johansson B. Adults with complex congenital heart disease have impaired skeletal muscle function and reduced confidence in performing exercise training. European Journal of Preventive Cardiology, e-published, 20 July 2014.

II. **Sandberg C,** Pomeroy J, Thilén U, Gradmark A, Wadell K, Johansson B. Habitual Physical Activity in Adults with Congenital Heart Disease Compared with Age- and Sex- Matched Controls. *Accepted* for publication in Canadian Journal of Cardiology August 2015.

III. **Sandberg C**, Rinnström D, Dellborg M, Thilén U, Sörensson P, Nielsen N-E, Christersson C, Wadell K, Johansson B. Height, weight and body mass index in adults with congenital heart disease. International Journal of Cardiology. 2015, 187:219-26.

IV. **Sandberg C,** Engström KG, Dellborg M, Thilén U, Wadell K, Johansson B. The level of physical exercise is associated with self-reported health status (EQ-5D) in adults with congenital heart disease. European Journal of Preventive Cardiology, 2015, 22(2):240-8.

V. **Sandberg C,** Hedström M, Wadell K, Dellborg M, Magnusson A, Zetterström AK, Ljungqvist A, Johansson B. Home-based interval training increases endurance capacity in adults with complex congenital heart disease. *Manuscript.*

Introduction

Adults with congenital heart disease are a growing population and today they outnumber the children with corresponding lesions [1, 2]. Since a congenital heart lesion may result in reduced exercise capacity, this population is a potential target for physiotherapy [3, 4]. However, improved knowledge of physical performance, physical activity, body composition and the effects of exercise training in this patient population is required.

Definition

Congenital heart disease can be defined as a structural or functional abnormality of the heart or the great vessels that is present at birth [5-7]. There are a large number of different diagnoses defined as congenital heart diseases. The definition is not strict and traditionally syndromes such as Marfan and Noonan are included while hereditary cardiomyopathies and arrhythmias generally are not included. Furthermore, bicuspid aortic valve, previously considered as an anatomic variation, is generally not included in the overall prevalence [8].

The most commonly used acronyms for adults with congenital heart disease are GUCH (grown-up congenital heart disease) and ACHD (adult congenital heart disease). GUCH was originally coined by Professor Jane Sommerville [9] and is most often used in the Nordic countries and in northern Europe while ACHD is used in northern America.

Etiology

The formation of the heart is a very complex process that takes place between the 18th day - 9th week of gestation. [10]. A deviation in this process may cause a defect in the heart or the great vessels, which in turn may alter further structural and functional development of the heart and circulatory system. In general, the etiology of congenital heart disease is regarded as multifactorial where both genetic and environmental factors plays a role [6, 11]. There are a number of congenital heart diseases with a known underlying genetic cause *e.g.* CATCH 22q11 deletion syndrome and Marfan syndrome. Some of these are inherited and others arise as spontaneous new mutations and the clinical presentation may vary from mild to severe [12]. In addition, environmental factor as maternal diabetes or exposure to toxins (e.g. alcohol, pharmaceuticals) may be involved [11]. Furthermore, if one of the parents has a congenital heart disease, the risk of recurrence in their

children is slightly raised but not necessarily with the same lesion as in the parent [6].

Prevalence

The prevalence of congenital heart disease is approximately 0.8% of live births worldwide and thereby one of the most common innate defects [6]. Due to differences in diagnostic modalities, the prevalence may vary between different regions of the world. In addition, socioeconomic factors, *e.g.* protection against rubella infection and exposure to toxins may play a role in the varying incidence of heart defects. Furthermore, the absolute number of babies born with congenital heart disease in developing countries is higher, due to larger populations in these countries. The prevalence later in life is affected by access to proper diagnostics, intensive care and surgical treatment. Without access to adequate care, the mortality rate due to congenital heart disease corresponds to the natural history of the disease [13, 14]. As a result of early diagnosis and intervention there are only occasional patients born with a shunt that develop Eisenmenger syndrome (pulmonary arterial hypertension secondary to congenital heart disease) in the industrialized countries. In contrast, the incidence in developing countries remains unchanged. The birth rate of children with congenital heart disease seems to be relatively unchanged over time. However, with improved prenatal diagnostics the termination rate due to complex heart lesions, *e.g.* hypoplastic left heart syndrome, has increased in some countries [15].

Classification and overview of diagnoses

Patients with congenital heart disease constitute a very heterogeneous group with a large number of different diagnoses. In addition, there is a large variability within every diagnosis group regarding severity of the lesion and presence of symptoms. Lesions are commonly classified as simple or complex lesions. Single lesions *e.g.* a shunt lesion or a valvular defect are often classified as simple lesions, while several defects in combination *e.g.* tetralogy of Fallot (ToF) (Figure 2) or dextro-transposition of the great arteries (d-TGA) are classified as complex lesions [7]. This classification also harmonizes with the expected reduction in exercise capacity [4]. An overview of congenital heart lesions and surgical interventions is presented in Table 1-4.

Surgical interventions

The majority of surgical interventions are performed during childhood. Thanks to medical and surgical advances, many congenital heart diseases are detected and treated earlier and with more appropriate techniques, which implies a shorter period under exposure of *e.g.* a pressure and volume overload of the heart or cyanosis. Furthermore, the number of children operated on for severe cardiac defects have increased and patients previously not possible to treat are now operated *i.e.* patients with HLHS are now treated using the Norwood procedure [7, 16]. In patients with d-TGA these advances has led to a shift in surgical technique from atrial switch, resulting in a physiological correction but with a systemic right ventricle (Figure 3), to arterial switch which results in an anatomical as well as physiological correction [17]. The surgical technique used for palliation with the Fontan principle has also developed continuously. In the original procedure, the right atrium was included as conduit for the venous return, which was associated with dilation of the right atrium with loss of kinetic energy, thrombus formation and arrhythmia [18, 19]. In the current techniques the atrium is by-passed via an extra-cardiac conduit anastomosed directly to the pulmonary arteries (Figure 4) [18, 20]. An overview of the common surgical procedures of respective lesion is presented in Table 3 and 4. A historical overview regarding surgical interventions relevant for congenital heart surgery is presented in Figure 1.

Prognosis

Thanks to the advances in medical and surgical treatment during the past decades the long-term survival has improved dramatically, especially among the patients with complex lesions [1, 7, 16]. Therefore, the number of adults with complex lesions currently is estimated to outnumber the children with corresponding lesions [1, 2]. Furthermore, the need for re-intervention has decreased [7]. Currently approximately 90% of children born with congenital heart disease in industrialized countries survive into adulthood (>18years) [21]. When analysing long-term survival (60-year follow-up) patients surgically corrected for ASD or PDA had a normal life expectancy in comparison to the general population. Patients corrected for CoA and VSD had slightly reduced survival rates at 50 years follow-up. Among patients with the most complex lesions, TGA and those palliated with Fontan/TCPC, surviving the first surgery seems to be the most critical part and in this population the long-term survival (45-50 years follow-up) was clearly reduced [16, 22].

Table 1. Congenital heart lesions classified as simple.

Diagnosis	Prevalence* SWEDCON	Anatomical defect	Pathophysiology
Atrial septal defect (ASD)	17.1%	Abnormal communication between the two atria through the atrial septum. There are several anatomical variants.	Shunting of oxygenated blood from left to right. Volume overload on both atria, the right ventricle and the pulmonary circulation.
Ventricular septal defect (VSD)	11.9%	Abnormal communication between the two ventricles through the ventricular septum. There are several anatomical variants.	Shunting of oxygenated blood from left to right. Volume overload on the pulmonary circulation and the left side of the heart.
Patent ductus arteriosus (PDA)	2.5%	Persistent flow through the arterial duct which otherwise normally closes short after birth.	Shunting of oxygenated blood from left to right. Volume overload on the pulmonary circulation and the left side of the heart.
Pulmonary stenosis (PS)	7.5%	Stenosis of the pulmonary valve.	Pressure overload on the right ventricle. In long-term dysfunction of the right ventricle.
Aortic stenosis (AS)	13.9%#	Stenosis of aortic valve, often associated with bicuspid aortic valve.	Pressure overload on the left ventricle. In long-term dysfunction of the left ventricle.
Aortic regurgitation (AR)		Regurgitation of the aortic valve is rarely present at birth but often a consequence of altered anatomy, geometry of supporting structures or direct damage to cusps.	Regurgitation of the aortic valve cause volume overload of the left ventricle.

Coarctation of the aorta (CoA)	10%	A local narrowing of the aorta located at the junction of distal aortic arch and the descending aorta just below origin of left subclavian artery, or a hypoplastic segment including the aortic arch or the aorta distal to the origin of the left subclavian artery. Often associated with bicuspid aortic valve.	Obstruction of blood flow depending on the degree of coarctation. Arterial hypertension in the upper part of the body.

*) Statistics of prevalence in adults with congenital heart disease was collected from the adult section of the Swedish registry of congenital heart disease (SWEDCON) (2014, n=11313). #; prevalence of AS and AR are combined for both of these diagnoses. The information on anatomy and pathophysiology and prevalence is based Diagnosis and Management of Adult Congenital Heart Disease, 2nd ed., Gatzoulis *et al.* 2011 [6], Braunwald´s Heart Disease a Textbook of Cardiovascular Medicine [11], Congenital Heart Disease in the Adult, Gersony and Rosenbaum, 2002 [18] and SWEDCON [2].

Table 2. Congenital heart lesions classified as complex.

Diagnosis	Prevalence* SWEDCON	Anatomical defect	Pathophysiology
Tetralogy of Fallot (ToF)	7.1%	VSD, RVOTO and as a consequence overriding aorta and hypertrophy of the right ventricle.	RVOTO with obstruction of pulmonary blood flow in combination with VSD leads to shunting (right to left) of deoxygenated blood with cyanosis and hypoperfusion of the lungs.
Transposition of the great arteries (d-TGA)	4.0%	The aorta and pulmonary artery are connected to the anatomically "wrong" ventricles.	This implies parallel lung- and systemic circulation, a condition not compatible with life. Need of emergent intervention.
Congenitally corrected transposition of the great arteries (ccTGA)	1.2%	The atrias are connected to the "wrong" ventricles and the aorta and pulmonary artery are connected to the anatomically "wrong" ventricles.	The morphologically right ventricle serves as the systemic ventricle but the circulation follows a normal route. These patients are not surgically corrected (which the terminology unfortunately implies).
Univentricular heart	1.3%	Due to the underlying heart defect (*e.g.* tricuspid atresia, double inlet left ventricle, hypoplastic left heart syndrome) a surgical correction to a two-chamber system has not been possible to create.	After complete surgery, the systemic venous return is led directly to the pulmonary arteries, and thus creating a passive pulmonary blood flow. Limited capacity to increase cardiac output and reduced exercise capacity.

Eisenmenger syndrome	na	Presence of a significant shunt lesion; VSD, PDA or ASD that causes increased pulmonary blood flow (left-to-right) which leads to structural reactions of the pulmonary vascular bed and increased vascular resistance. If the shunt not is closed in time, the pulmonary resistance continues to rise and fixed pulmonary hypertension and reversal of the shunt (right-to-left) may follow. At this point closure of the shunt is not possible.	Cyanosis and marked reduction of exercise capacity even at low physical activity level.

Statistics of prevalence in adults with congenital heart disease are collected from the adult section of the Swedish registry of congenital heart disease (SWEDCON) (2014, n=11313). RVOT; right ventricular outflow tract, RVOTO; right ventricular outflow tract obstruction, VSD; ventricular septal defect, PDA; persistent ductus arteriosus, ASD; atrial septal defect, na; not applicable. The information on anatomy and pathophysiology and prevalence is based Diagnosis and Management of Adult Congenital Heart Disease, 2nd ed, Gatzoulis *et al.* 2011 [6], Braunwald´s Heart Disease a Textbook of Cardiovascular Medicine [11], Congenital Heart Disease in the Adult, Gersony and Rosenbaum, 2002 [18] and SWEDCON [2]

Table 3. Summary of interventions used in patients with simple congenital heart disease.

Diagnosis	Intervention
Atrial septal defect (ASD)	Transcatheter device closure of the septal defect may be used in ASD secundum, if anatomically unfavourable or in other types of ASD, open heart surgery is needed. Most patients are diagnosed and treated during childhood but a significant number present in adulthood.
Ventricular septal defect (VSD)	Significant non-restrictive VSD is closed during childhood to prevent left ventricular failure, pulmonary vessel disease and as a consequence development of Eisenmenger syndrome. A small restrictive VSD is left without intervention and may also close spontaneously. Open heart surgery with a patch is a common procedure.
Patent ductus arteriosus (PDA)	A PDA is closed early in childhood to prevent development of the Eisenmenger syndrome. Device closure of the duct is the most common technique but there are other options.
Pulmonary stenosis (PS)	In childhood, balloon dilatation of the valve is the most common procedure. Surgical valvulotomy or valve replacements are alternatives if the valve is calcified or dysplastic.
Aortic stenosis (AS)/ Aortic regurgitation (AR)	In young patients with symptomatic stenosis balloon aortic valvuloplasty or valvular commisurotomy are alternatives if no significant calcification or regurgitation is present. The Ross procedure where the aortic valve is replaced with the autologous pulmonary valve, which in turn is replaced with a homograft, may be used when no other procedure is feasible. In adult patients, aortic valve replacement with a mechanical prosthetic valve is preferred. The choice of surgical approach depends on the underlying pathological process and patient factors *e.g.* age, sex.
Coarctation of the aorta (CoA)	Catheter intervention including angioplasty and/or stent implantation is the most common alternatives in adults. There are a number of surgical techniques (*e.g.* end-to-end anastomosis, subclavian flap, interposition graft) applied according to the nature, site and extent of the coarctation.

The information in the table is based on Diagnosis and Management of Adult Congenital Heart Disease, 2nd ed, Gatzoulis *et al.* 2011 [6], Braunwald´s Heart Disease a Textbook of Cardiovascular Medicine [11] and Congenital Heart Disease in the Adult, Gersony and Rosenbaum, 2002 [18].

Table 4. Summary of surgical interventions used in patients with complex congenital heart disease.

Diagnosis	Surgical intervention
Tetralogy of Fallot (ToF)	Repair of VSD with a patch. Relief of RVOTO (valvotomy, resection of infundibular muscle bundles often in combination with a RVOT patch or a transannular patch to widen the outflow tract) (Figure 2).
Transposition of the great arteries (d-TGA)	The first step is usually to surgically create an ASD (via Raskind procedure or Blalock-Hanlon atrial septectomy) to provide mixing of pulmonary and systemic venous return. **Atrial correction** (Mustard/Senning procedure): in order to connect the pulmonary and systemic circulation in series, the blood flow is redirected via "tunnels", divided by a "baffle", in the atrias leaving the morphologically right ventricle to serve as the systemic ventricle (Figure 3). **Arterial switch procedure** (method used in Sweden since early 1990´s): the position of the aorta and pulmonary artery are switched and the coronary arteries re-implanted, resulting in an anatomical and physiological correction.
Congenitally corrected transposition of the great arteries (ccTGA)	Only a small number of patients are corrected with a double switch operation, a combination of atrial switch and arterial switch. No data on adults available.
Tricuspid atresia (TA), double inlet left ventricle DILV and other complex lesions *e.g.* HLHS* where surgical correction to a biventricular system not is feasible	Classic Fontan procedure, modified Fontan procedure or total cavo-pulmonary connection (TCPC). In patients with HLHS, the Norwood procedure is performed prior to the TCPC operation. As a consequence of all interventions, the venous return is directed to the pulmonary arteries. There is no subpulmonary ventricle. The main advantage is that volume overload on the ventricle (and pulmonary circulation) is relieved and that arterial oxygen saturation usually is in the normal range. The long-term prognosis of the currently used techniques is essentially unknown (Figure 4).
Eisenmenger	Not applicable. When fixed pulmonary hypertension is established, intervention is harmful.
Ebstein anomaly	Tricuspid valve repair. Tricuspid valve replacement. If the atrialised part of the right ventricle is severely dilated plication (or actual excision) of the right ventricle can be an option. In some cases, a bidirectional cavo-pulmonary shunt ("hemi-Fontan") is performed to reduce the venous return to the right ventricle.

HLHS; Hypoplastic left heart syndrome, RVOT; right ventricular outflow tract, RVOTO; right ventricular outflow tract obstruction, ASD; atrial septal defect. The information is based on Diagnosis and Management of Adult Congenital Heart Disease, 2nd ed, Gatzoulis *et al*. 2011 [6], Braunwald´s Heart Disease a Textbook of Cardiovascular Medicine [11] and Congenital Heart Disease in the Adult, Gersony and Rosenbaum, 2002 [18].

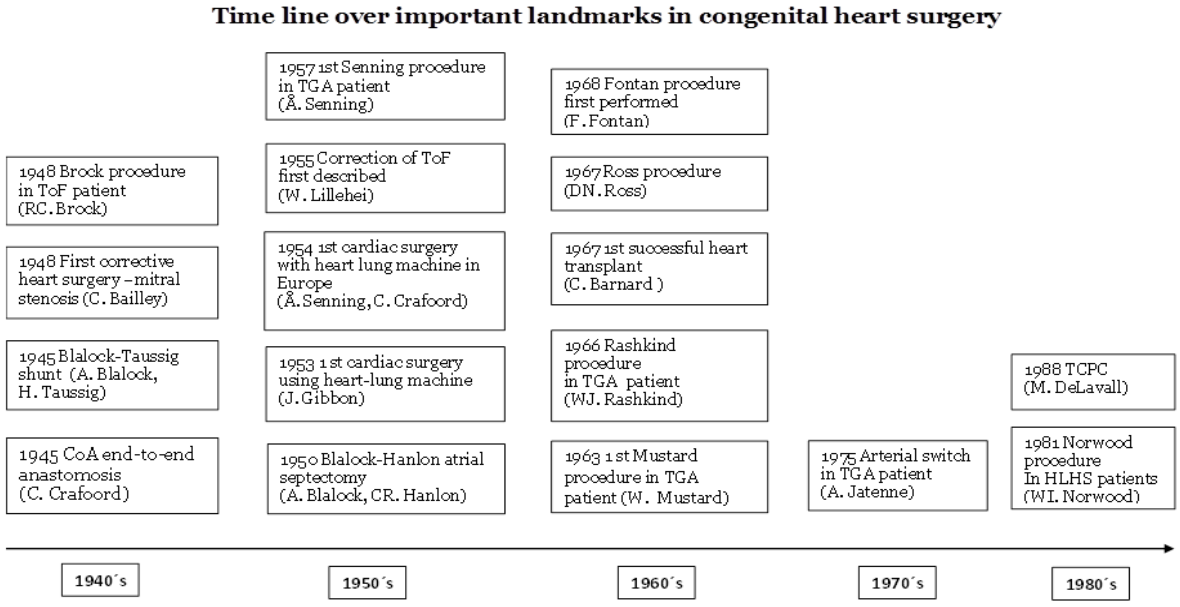


Figure 1. Time line over important landmarks in congenital heart surgery [23-39].

Follow-up

The need for follow-up varies between the different diagnoses. In some simple lesions, *e.g*. after a successful closure of an ASD during childhood, the patient can be considered as cured and will not need follow-up in adult age. When considering the more complex lesions, patients will need regular follow-up at specialized clinics. The main reason for this is to detect signs of deterioration or need for re-intervention at an early stage [40].

Physical performance

Exercise capacity

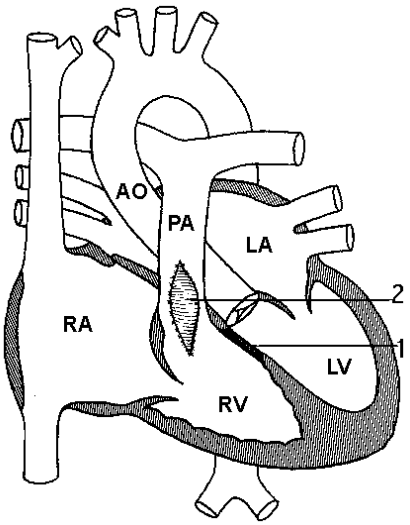
Exercise capacity is defined as the "maximum exertion that a person can sustain" [41] and is an overall measure of cardiac, pulmonary and metabolic function [42]. Measures of exercise capacity hold an important prognostic marker [3]. In general, adults with congenital heart disease have a reduced exercise capacity in comparison to healthy peers, which makes them a potential target for physiotherapy. The degree of impairment varies within the different diagnosis groups and may reflect the severity of a lesion *e.g*. the degree of aortic stenosis. In addition, the reduction in exercise capacity becomes more pronounced with increased complexity of the lesion, ranging from normal or mildly impaired in patients with simple lesions to severely impaired in those with complex lesions [3, 4, 43]. Just like in the general population, the exercise capacity declines over time [42, 44] but in patients with heart disease this may also be a symptom of deterioration [3, 6, 11]. The underlying cause for impaired exercise capacity is due to multiple factors, both cardiac and extra cardiac [6, 45, 46]. Moreover, many patients overestimate their actual physical capabilities [47].

Parallels are often drawn between patients with congenital heart disease and patients with congestive heart failure due to many physiological similarities. However, congestive heart failure often occurs late in life whereas the patients with congenital heart disease are exposed to altered circulatory physiology during a much longer period of time, which should be considered. This also means that a relatively mild heart defect over time may cause long-term adverse effects [6, 46].

Ventricular function

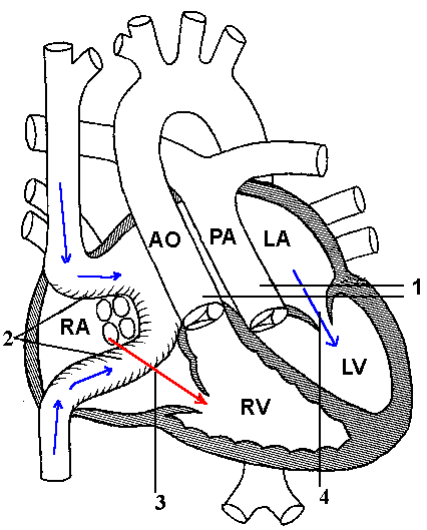
The systolic function of the ventricles may be affected due to a number of causes and may also decline over time. A stenosed or regurgitant valve, a shunt lesion or hypertension in the systemic or pulmonary arterial circulation can result in a hemodynamic overload of one or both ventricles. Because of this overload, ventricular dysfunction can develop over time and in severe cases cause overt heart failure [6, 46]. The effects of diastolic dysfunction on exercise capacity is however less studied, but in a hypertrophic ventricle, the diastolic relaxation is usually impaired, which negatively affects the diastolic filling and thereby also the cardiac output [6].

Figure 2. Tetralogy of Fallot post intervention.



1. Patch closure of ventricular septal defect
2. Right ventricular outflow/main pulmonary artery outflow patch (transannular patch)

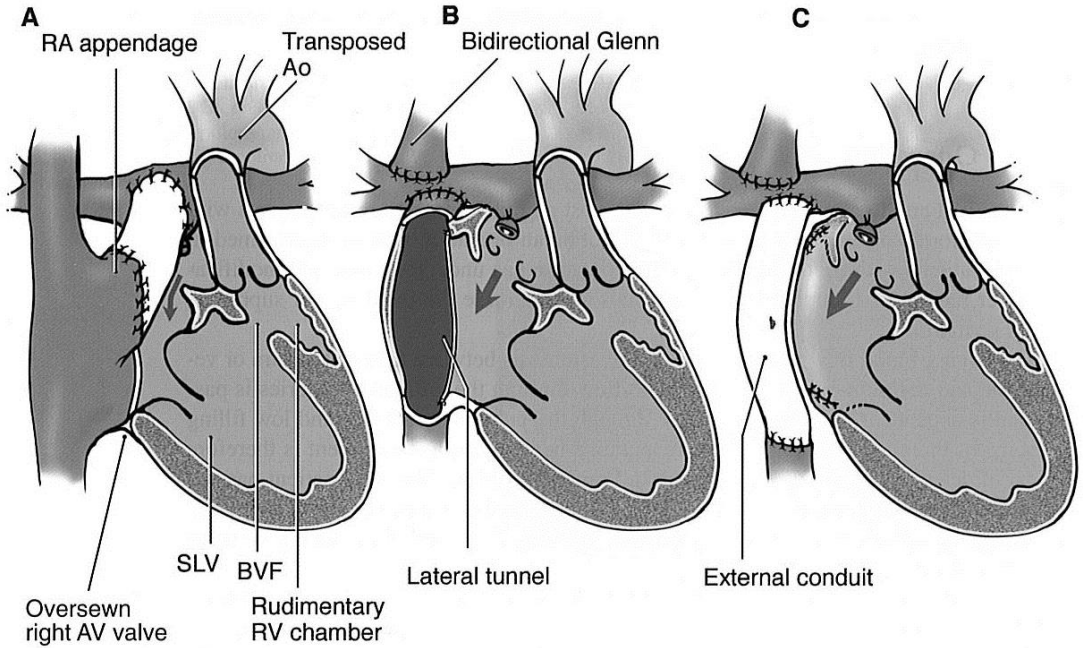
Figure 3. Dextro-transposition of the great arteries after Mustard procedure.



1. Transposition of the great arteries
2. Systemic venous channels created by an intra-atrial baffle.
3. Pulmonary vein flow through the tricuspid valve to the right ventricle
4. Systemic venous return through the mitral valve to the left ventricle

Selected illustrations from Mayer D, and Mullins C, *Congenital Heart Disease, A Diagrammatic Atlas*. New York: Alan R. Liss, Inc, 1988. http://www.achd-library.com. Reprinted with permission from John Wiley & Sons Ltd., UK.

Figure 4. Illustrations of anatomy after Fontan operation and total cavo-pulmonary connection.



A) The classic Fontan operation illustrated in a patient with, a single left ventricle, ventricular septal defect, hypoplastic right ventricle and transposition of the great arteries. The right atrial appendage is broadly anastomosed to the pulmonary artery. The right atrioventricular valve and atrial communication is closed. Oxygenated blood reaches the single ventricle and aorta via an atrioventricular valve and a ventricular septal defect. The single ventricle serves as the systemic ventricle. B) Total cavo-

pulmonary connection with a bidirectional Glenn anastomosis between the superior vena cava and the right pulmonary artery. The inferior vena cava connects with the right pulmonary artery via a “lateral tunnel” within the atrium. C) Total cavo-pulmonary connection where the inferior vena cava connects to the pulmonary artery via an external, interposed conduit. The arrows show the route of oxygenated blood from the pulmonary arteries to the systemic ventricle. RV; right ventricle, RA; right atria, AV; atrioventricular, BVF; bulboventricular foramen (= ventricular septal defect), Ao; aorta, SLV; single left ventricle. Illustration from Gersony W, Rosenbaum M, Congenital Heart Disease in the Adult, 2002 [18]. Reprinted with permission from the McGraw-Hill Companies, Inc., US.

The interaction between the ventricles is also important. As an example hypertrophy of the right ventricle, due to obstruction of the right ventricle outflow tract (RVOT) or in Ebsteins anomaly, can affect the left ventricular diastolic filling by changing the septal movement during diastole [6, 46, 48] . The ventricular function can also be affected by multiple open-heart surgeries especially if performed in an era of less developed cardio-protection. In the current era, the time to surgical corrective or palliative surgery is shorter [16]. This leads to decreased exposure to cyanosis and hemodynamic overload and thus less negative effects on ventricular function [49].

In adults with d-TGA corrected with Mustard/Senning procedures or in ccTGA, the morphologically right ventricle serves as the systemic ventricle. The morphologically right ventricle is not designed to handle the systemic pressure load over time. The myocytes in the morphologically left ventricle are arranged spirally around the ventricle. This gives the left ventricle a twisting motion during the systolic and early diastolic phase, which enables the left ventricle to sustain the necessary demands of a systemic ventricle. This arrangement of myocytes is not present in the morphologically right ventricle, which thereby is not suited to sustain the demands in the systemic position over a long period of time [45, 50]. In addition, the intra-atrial baffles in patients corrected with Mustard/Senning procedure can be relatively narrow and stiff, which may cause decreased preload and thereby decreased ability to increase stroke volume during exercise. In some of these patients, leakage of the baffles with shunting of blood, right to left, may occur with desaturation during exercise as a consequence [51]. Furthermore, the coronary artery supply and capillarisation of the morphologically right ventricle is not dimensioned for a systemic position, which in turn has a negative effect on the ventricular function [46, 52, 53]. Impaired myocardial perfusion has also been observed in patients with d-TGA corrected with the contemporary arterial switch operation [46, 53].

In patients palliated with Fontan/TCPC procedure, the systemic venous return is routed directly to the pulmonary arteries. The lack of sub-pulmonary ventricle affects the diastolic filling of the systemic ventricle and thereby the ability to increase the stroke volume with increased workload [45, 54]. During rest, inspiration facilitates the venous return while the peripheral muscle pump seems to be the more important factor during exercise [55]. In addition, an impaired contractile response with increased heart rate has been observed [56].

Heart rate

Chronotropic incompetence, defined as inability to increase heart rate >80% of predicted maximum heart rate, is rather common in the population of adults with congenital heart disease. A prevalence of 34-62% of chronotropic incompetence has been reported in patients with congenital heart disease [46, 57-59]. This is a larger proportion in comparison to patients with coronary artery disease or congestive heart failure [58]. Impaired ability to increase the heart rate with increased workload may lead to decreased exercise capacity [45, 46, 59]. The cause of chronotropic incompetence can be due to an intrinsic malfunction of the conduction system (usually sick sinus node), caused by medication (ß-blockers), injury of the sinus- or atrioventricular node during intervention or due to chronic pacing [59]. Chronotropic incompetence is more common in complex lesions *e.g*. patients palliated with Fontan/TCPC procedure and TGA. Due to lack of a sub-pulmonary ventricle, patients palliated with Fontan/TCPC procedure are in general more dependent on increase in heart rate to enhance cardiac output [60]. Together with other measures of heart rate response to exercise, such as heart rate reserve (peak heart rate – resting heart rate) and heart rate recovery (the rate of decrease in heart rate after cessation of exercise), chronotropic incompetence is an important prognostic marker in adults with congenital heart disease [57]. Heart rate response, during and after exercise reflects cardiac autonomic activity. The increase in heart rate during activity reflects the withdrawal of parasympathetic and increase of sympathetic activity. Furthermore, the early decrease in heart rate after activity cessation reflects the parasympathetic reactivation. In adults with congenital heart disease, blunted increase in heart rate during activity and slower heart rate recovery after activity cessation has been observed as an effect of altered autonomic function [61]. Previous heart surgery, with injury of nerves, is one of the main causes of autonomous dysfunction in this population [62-64].

Pulmonary function

Impaired pulmonary function (forced expiratory volume in one second, FEV_1 and forced vital capacity, FVC) may also contribute to a decreased exercise capacity in patients with congenital heart disease [3, 46, 65]. Moreover, impaired pulmonary function is more common in patients with complex lesions [66]. In patients with lesions causing decreased pulmonary blood flow before corrective or palliative surgery, *e.g*. tetralogy of Fallot, this may result in hypoplasia of the pulmonary vessels and alveoli [67, 68]. Patients palliated with Fontan/TCPC procedure have also been observed to have hypoplastic lungs [45]. Furthermore, repeated open-heart surgeries may lead to increased stiffness of the lungs and thereby restrictive lung function [69,

70]. In addition, during cardiac surgery the vagal nerve may be injured causing postoperative dysfunction of the diaphragm [71].

Pulmonary blood flow

The pulmonary blood flow may be altered in congenital heart disease. In presence of an RVOTO, the ability to increase pulmonary blood flow during exertion is limited and thereby also the capacity to increase cardiac output is affected [72]. In patients palliated with Fontan/TCPC procedure, the ability to increase pulmonary blood flow during exertion is diminished due to lack of a sub-pulmonary ventricle. Moreover, increased pulmonary arterial blood pressure, as seen in its extreme form in patients with the Eisenmenger syndrome, may severely limit the exercise capacity [65]. A common finding in patients with congenital heart disease is impaired ventilatory efficiency, expressed as increased VE/VCO_2 slope during exercise testing. Hypoperfusion of the lungs, physiologic dead-space due to right-to-left shunting and enhanced respiratory reflex sensitivity are suggested to be potential contributors of reduced exercise capacity in patients with complex lesions [6, 46, 59, 65].

Muscle function

In patients with congestive heart failure muscle wasting is common and an important prognostic marker [73-75]. Impaired muscle strength is also a strong predictor of mortality [73, 76]. The skeletal muscle abnormalities causing impaired muscle strength in patients with congestive heart failure are *e.g*. impaired muscle energy metabolism, fibre-type transition and decrease in muscle fibre size [77, 78]. Recently, impaired muscle metabolism and reduced skeletal muscle mass has been reported in adults palliated with Fontan/TCPC procedure [79]. This phenomenon of impaired muscle function has previously been reported in children with corresponding heart lesions [45]. In addition, muscle weakness and reduced muscular endurance has been described in patients with congenital heart lesions of different complexity [80-82]. Furthermore, an association between reduced muscle strength and exercise capacity has been observed [80].

Physical activity

Physical activity is defined as “any bodily movement produced by skeletal muscles that results in energy expenditure” [83]. The positive link between physical activity and health in the general population is well established. One of the first studies to report of this connection was performed on busses in London. The incidence of cardiovascular disease was higher in bus drivers compared to the conductors who climbed up and down the stairs of the bus to collect tickets [84]. Today sedentary lifestyle has emerged as an important risk factor for cardiovascular disease and mortality [85-87]. According to the current recommendations by the World Health Organization (WHO) on physical activity for adults (aged 18-64), at least 150 minutes of moderate physical activity per week or 75 minutes of vigorous physical activity is advocated. The activity should be performed in bouts of at least 10 minutes and because of the dose-response relationship, additionally increased physical activity time further enhances the positive effects [88].

Monitoring physical activity

When monitoring physical activity it is important to gather information about the mode, frequency, duration and intensity of the activity [89-91]. Furthermore, when assessing total physical activity it is important to cover the four common domains occupational, domestic, transportation and leisure time physical activity [91]. Physical activity results in increased energy expenditure and the increase is closely linked to the intensity of the activity [89, 91]. There are a number of methods that are used to quantify energy expenditure *e.g.* metabolic equivalent (MET, 1 MET=resting energy expenditure 3.5 ml O_2/kg/min), kilocalories (kcal, 1 liter of O_2 consumption $\approx$5 kcal of energy) and time spent in different intensities of physical activity. When assessing the amount of time spent at a specified intensity, *e.g.* moderate activity level, the intensity can be absolute or relative. Absolute intensity refers to the external work performed *e.g.* 3.0-5.9 MET which correspond to a moderate intensity. While relative intensity is determined in relation to exercise capacity *e.g.* percent of VO_2 max or percent of peak heart rate [89].

Monitoring physical activity in patients with congenital heart disease

In a recent report where physical activity level was assessed using an accelerometer, young children with congenital heart disease were equally active as their age-, sex- and seasonally- matched peers. Moreover, the majority, of patients as well as controls, did not reach the current

recommendations on physical activity for children [92]. In a group of adolescents corrected with Fontan procedure or with tetralogy of Fallot approximately 30 percent did not reach these recommendations [93]. In adults with congenital heart disease the physical activity level has been reported to be correlated to exercise capacity [94]. Furthermore, Dua *et al* showed that the great majority did not reach the current recommendations on physical activity in adults while Müller *et al* showed the opposite [94, 95].

Subjective methods

Physical activity questionnaires are subjective methods commonly used to evaluate physical activity. There are a large number of different questionnaires on physical activity. *Global physical activity questionnaires* give a crude overview of a person's activity level. They often consist of few items and can roughly discriminate if a person is inactive, insufficiently active or sufficiently active. Such instruments are common as a part of extensive health questionnaires [96]. *Short recall physical activity questionnaires*, provides an overview of the total volume of physical activity during the past week. Furthermore, results of these questionnaires often provide an activity score with a higher score indicating more physical activity [89, 91]. The International Physical Activity Questionnaire (IPAQ) is an example of a short recall physical activity questionnaire [97]. Further methods used to investigate self-reported physical activity, are diaries or activity logs were the type and time of activity are registered. Currently this can be performed using *e.g*. a smartphone [91]. Questionnaires can be used at low cost and reach a large number of persons. Common and well-known problems with self-reported physical activity are recall bias or social desirability bias [90]. It has previously been shown that physical activity of moderate intensity was more accurately reported than activities of lower intensity when using questionnaires [91]. Moderately intense activities were thought to be easier to recall and the questionnaires were unable to capture light activities [98].

Objective methods

Indirect calorimetry

Indirect calorimetry is regarded as the reference method when measuring energy expenditure. The most common method is to analyse the amount of O_2 consumed and CO_2 produced during breathing of room air or a known mixture of gases. This method is used in a laboratory and there are different systems available [89].

Doubly labelled water

The doubly labelled water method is used to assess the total energy expenditure in free-living over one to three weeks. Water containing a known amount of two stable isotopes (oxygen-18 and deuterium) is ingested. The difference in elimination time between these isotopes is then used to calculate the CO_2 production and thereby energy expenditure over the measured time [89]. This method has also been used as validation method for different accelerometers [99].

Wearable activity monitors

There are a number of different wearable monitors available to objectively assess physical activity. At present there is no golden standard monitor to measure habitual physical activity [89, 91, 100].

Pedometers

The pedometers currently on the market have far more advanced technology compared to the first generation devices. Microelectromechanical systems (MEMS) and specific algorithms are used to translate the signalling into steps, which has improved their accuracy. Most of the pedometers are hip-worn and the accuracy of step counts has been reported to be slightly less accurate at lower walking speeds ≤3km/h. Pedometers can be used to assess physical activity at low cost and on a large number of individuals. It can also be used to motivate people. On the other hand, a pedometer cannot measure activity mode and the accuracy varies between different monitors [89, 91, 100]. An overview of commonly used pedometers is presented in Table 5.

Accelerometers

Accelerometer monitors are also considered as MEMS systems. The monitor registers acceleration/deceleration due to gravity during physical activity. The acceleration/deceleration can be measured uniaxial (usually vertical) or triaxial (vertical, mediolateral and anterior-posterior). The outcome from recording of acceleration/deceleration, often referred to as raw accelerometer data (acceleration m/s^2), is further transformed to counts (counts/minute or total counts per day). Furthermore, to specify energy expenditure (MET, kcal) or time spent at different intensities of physical activity, monitor specific prediction equations or counts are used. It is important to be aware of that the prediction equations and cut-offs for

counts used to identify physical activity levels differ between types of monitors. Accelerometers are relatively inexpensive, provides detailed information on intensity, frequency and duration of the activity and data can be stored for weeks at a time. However, activities like cycling or climbing stairs cannot be accounted for. Furthermore, if the monitor is hip worn, the upper-body movements will be neglected [89, 91, 100]. An overview of commonly used accelerometers is presented in Table 6.

Heart rate monitors

Using heart rate as a method to assess physical activity is based on the linear relationship between increased heart rate with increased physical activity. This relationship is however stronger at moderate to vigorous activities. Heart rate monitors often consists of electrodes in a chest worn strap that signals wireless to a wrist worn monitor. To achieve best possible measurements, calibration of the individual heart rate and oxygen consumption at different levels of activity should be performed prior to the monitoring period. Stimuli like emotions and medication can affect the heart rate and thereby bias the registrations [89, 91, 100].

Multi-sensing monitors

Multi-sensing monitors have combined multiple mechanical with physiological monitors *e.g*. accelerometer and heart rate monitor in purpose to collect more accurate data on energy expenditure and physical activity. These monitors are often more expensive and can be more inconvenient to wear. In addition, each sensor may contribute with measurement error and with additional complexity the risk of technical problems may increase [89, 91, 100]. An overview of commonly used multi-sensing monitors is presented in Table 7.

Table 5. Commonly used pedometers

	Omron	**StepWatch**
Placement	Hip, pocket, chest	Ankle
Sensor	Accelerometer	Accelerometer
Outcome measures	Steps, aerobic steps (>60steps/min or walking >10 min continuously), energy expenditure, distance	Steps, gait parameters
Website	www.omronhealthcare.com	www.orthocareinnovations.com

Min; minutes. Modified after Strath *et al.* Circulation 2013 [89].

Table 6. Commonly used accelerometers.

	Actical	**ActiGraph**	**ActivPAL**	**RT3**
Placement	Hip, wrist , ankle	Hip, wrist , ankle	Thigh	Hip
Number of axes	Omnidirectional	Triaxial	Uniaxial	Triaxial
Modes of sampling	Raw acceleration + steps	Raw acceleration	Raw acceleration	Counts
Outcome measures	Physical activity energy expenditure, steps	Energy expenditure, steps, physical activity intensity, body position	Sitting/lying, standing time, steps, step rate, number of posture changes, MET hrs, Physical activity level	Energy expenditure, MET, activity counts
Website	www.philips.com/actical	www.theactigraph.com	www.paltechnologies.com	www.stayhealthy.com

MET; metabolic equivalent, hrs; hours. Modified after Strath *et al.* Circulation 2013 [89].

Table 7. Commonly used multi-sensing monitors

	Actiheart	**SenseWear**
Placement	Chest	Upper arm
Sensor	Uniaxial accelerometer, heart rate sensing	Triaxial accelerometer, galvanic skin temperature and response, heat flux sensing
Number of axes	Uniaxial	Triaxial
Modes of sampling	Raw acceleration	Raw signals
Outcome measures	Physical activity energy expenditure, moderate-to-vigorous intensity time	Energy expenditure, moderate-to-vigorous intensity time, steps, MET
Website	www.camntech.com/products/actiheart	www.sensewear.bodymedia.com

MET; metabolic equivalent. Modified after Strath *et al.* Circulation 2013 [89].

Exercise training

Exercise training can be defined as "physical activity that is planned, structured and repetitive and aims to increase or maintain physical fitness" [83]. Exercise training is a method used by physiotherapists in rehabilitation of patients with acquired and congenital heart disease. Important principles to take into account when setting up an exercise training protocol are "the principle of specificity", what is practiced on will be improved, "the principle of progressive overload", an overload must be achieved in order to achieve a compensatory increase of exercise capacity or strength and finally "the principle of individuality", *e.g.* the individual capacity must be considered. Furthermore training mode, frequency, duration and intensity must be determined [101].

Continuous moderate aerobic exercise training or interval training are training modes that can be used in order to increase exercise capacity. In patients with congestive heart failure, the effects of exercise training has been extensively investigated and reported to be safe and to improve several health related factors. Furthermore, exercise training with a higher intensity which is possible to accomplish with interval training, improved exercise capacity more than continuous training at moderate intensity in patients with congestive heart failure [102-104].

Exercise training in children and adolescents with congenital heart disease has been reported to be safe and to improve fitness. However, this is a heterogeneous group of patients with a large variety in exercise capacity [3, 4]. Furthermore, the knowledge of the effect on specific diagnosis groups and the effects on the heart is lacking and therefore recommendations of exercise training are difficult to summarize [105, 106]. The current recommendations, where individualised exercise prescription is enhanced, are mainly based on consensus by expertise [107]. Relatively few intervention studies have investigated the effects of exercise training among adults with congenital heart disease. Furthermore, the majority of these studies have focused on only one diagnosis group. In conclusion, these studies indicate that exercise training is safe, and improves exercise capacity without adverse effects on cardiac function [80, 108-117]. An overview of intervention studies evaluating the effects of exercise training studies among adults with congenital heart disease is presented in Table 8-10.

Cardiopulmonary exercise testing (CPET) is commonly used to evaluate exercise capacity and change in exercise capacity as result of exercise training. CPET is usually performed using either an ergometer cycle or a motorised treadmill [118, 119]. Peak oxygen up-take, peak workload and test duration are common outcome variables used in exercise training studies.

Table 8. Study design of exercise training studies in adults with congenital heart disease.

Reference	Study design	Study population I/C	Diagnosis	Age	Duration weeks	Sessions/ week	Duration minutes	Intensity	Training Mode
Brassard (2006)	non RCT	9 (5/4)	Fontan	11-26	8	3	20-30	50-80% peak VO_2	Ergometer cycle Resistance training
Cordina (2013)	RCT	11 (6/5)	Fontan	31±4/32±4	20	3	60	8 rep 3 set	Resistance training
Dua (2010)	Cohort	61	Mixed	31.7±10.9	10	5-7	5-30	Individual incremental	Walking
Duppen (2014, 2015)	RCT	56/37	ToF, Fontan	10-25	12	3	60	60-70% of HRR	Aerobic exercise
Duppen (2015)	RCT	28/20	ToF	10-25	12	3	60	60-70% of HRR	Aerobic exercise
Martinez-Quintana (2010)	Non-RCT	8	CHD+PAH	18-37	12	2	34	80% peak HR at 6 MWT	Ergometer cycle (intervals)
Minamisawa (2001)	Cohort	11	Fontan	19±4	8-12	2-3	26-36	60-80% peak HR	Brisk walking or jogging

Shafer (2015)	Non-RCT	14/9*	TGA with SRV	34.0±10.0	12	4-6	30-60	60-95% peak HR	Walking + Aerobic continuous + interval
Therrien (2003)	RCT	9/8	ToF	35.0±9/ 43.3±7.3	12	3	30-50	60-85%peak VO_2	Ergometer cycle Treadmill + outdoor walking
Westhoff-Bleck (2013)	RCT	24/24	TGA with SRV	29.3±3.4	24	3-5	10-30	50% peak VO_2	Ergometer cycle Resistance training
Winter (2010)	RCT	24/22	TGA with SRV	32±11	10	3	42	75-90% peak HR	Interval Step aerobic

I/C; Intervention group/control group, RCT; randomised controlled study, CHD; congenital heart disease, PAH pulmonary arterial hypertension, TGA; transposition of the great arteries; SVR; systemic right ventricle, ToF; tetralogy of Fallot, HR; heart rate, HRR; heart rate reserve. *) denotes healthy controls that also followed the exercise training protocol [80, 93, 108-117].

Table 9. Test method and outcome

Reference	Test method	Outcome
Brassard (2006)	CPET ergometer cycle. Neuromuscular function.	No change in peak $VO_{2..}$ No change in neuromuscular function.
Cordina (2013)	CPET ergometer cycle. Strength test. Total body DEXA. Calf MRS.	Peak VO_2 increased with 9.5% 183±31 ml/min. Strength increased 43±7%. Increased total lean body mass 1.94±0.52 kg. No change in calf MRS.
Dua (2010)	CPET treadmill. QoL.	Regular walking is feasible. Increased duration at treadmill exercise test 21.7% (2 min). Improved QoL.
Duppen (2014, 2015)	CPET ergometer cycle.	Peak work load increased 4.6% in intervention group compared to controls (6.9±11.8 W *vs.* 0.8±13.9W, p=0.047). Peak VO2 increased 5.0% within the intervention group (1.7±4.2 ml/kg/min, p=0.011) but not compared to controls (0.9±5.2 ml/kg/min, ns).
Duppen (2015)	CPET ergometer cycle.	Peak work load increased 4.9 % in intervention group compared to controls (8.4±11.4 W *vs.* -0.1±15.9W, p=0.048). Peak VO2 increased within the intervention group mean (2.9±4.0 ml/kg/min, p=0.002) but not compared to controls (0.7±5.1 ml/kg/min, p=0.14).

Martinez-Quintana (2010)	6MWT. Pedometer. Hand grip strength. Isometric strength of quadriceps. QoL.	No change of any outcome variable.
Minamisawa (2001)	CPET ergometer cycle.	6.8% (1.7ml/kg/min, p=0.029) increase in peak VO_2.
Shafer (2015)	CPET treadmill.	5.7% (1.3 ml/kg/min, p=0.05) increase in peak VO_2.
Therrien (2003)	CPET ergometer cycle.	10% (2.2ml/kg/min, p=0.049) increase in peak VO_2 in intervention group but not compared to controls. Exercise training is safe.
Westhoff-Bleck (2013)	CPET ergometer cycle.	15.8% (3.8 ml/kg/min, p=0.001) increase in peak VO_2 in comparison to controls.
Winter (2010)	CPET ergometer cycle. QoL.	12.6% (3.4ml/kg/min, p=0.04) in comparison to controls. No change in QoL.

CPET; cardiopulmonary exercise test, DEXA; dual energy X-ray absorptiometry, MRS; muscle phosphorous spectroscopy, QoL; Quality of life, 6 MWT; 6 minute walk test, ns; not significant [80, 93, 108-117].

Table 10. Evaluation and outcome of cardiac effects of exercise training.

Reference	Evaluation of cardiac status	Outcome
Brassard P (2006)	-	-
Cordina (2013)	Cardiac MRI.	Improved cardiac filling and cardiac output. Reduced dependence on respiration for venous return.
Dua (2010)	ECG. Echocardiography.	No results mentioned.
Duppen (2014, 2015)	Cardiac MRI, Echocardiography and Neurohormones.	No evidence of adverse effects on cardiac function.
Duppen (2015)	Cardiac MRI, Echocardiography.	No evidence of adverse effects on cardiac function.
Martinez-Quintana (2010)	NT-proBNP.	No change.
Minamisawa (2001)	-	-
Shafer (2015)	High sensitive Troponin-T, NT-proBNP, echocardiography and Cardiac MRI.	No evidence of adverse effects on the sub-pulmonary right ventricle.
Therrien (2003)	-	-
Westhoff-Bleck (2013)	Cardiac MRI.	No change in subaortic right ventricle dimensions as signs of deterioration.
Winter (2010)	NT-proBNP.	No changes.

MRI; magnetic resonance imaging, ECG; electrocardiogram, NT-proBNP; N-terminal pro-brain natriuretic peptide [80, 93, 108-117].

Body mass index

Body mass index is the measure of weight-for-height (kg/m^2) and is used to classify underweight, overweight and obesity. BMI values are independent of age and the same classification is used for both sexes. BMI ≤18.5 is classified as underweight, BMI ≥25 is classified as overweight and BMI≥30 as obese [120]. Overweight and obesity is a growing problem not only in industrialized countries, it is an emerging problem in the developmental countries as well [121, 122].

There are reports of an increasing prevalence of obesity in children and adolescents with congenital heart disease [123-126]. Overweight/obesity is a well-known cardiovascular risk factor and predictor of all-cause mortality [127, 128]. When considering the prevalence of overweight in adults with congenital heart disease, data are scare and contradictory. In a study on prevalence of cardiovascular risk factors in adults with congenital heart disease, the prevalence of obesity (BMI≥30) was somewhat higher compared to controls. Furthermore the prevalence of overweight (BMI≥25) was equal as in controls [129]. In contrast, a lower prevalence of overweight/obesity has been reported by others [130]. BMI is an easy accessible measure to estimate the prevalence of overweight/obesity in a large population. However, estimation of overweight/obesity using BMI can be questioned, as it does not provide any information on true body composition. In an athletic person with a high BMI due to large muscle mass there is a risk of misclassification [131, 132]. On the other hand, in the general population there is only a small proportion expected to be active on a level that gives high BMI due to a large muscle mass [133].

NYHA classification

The New York Heart Association classification system is used to classify patient into four categories due to symptom presence and limitations, *e.g.* shortness of breath, during physical activity (Table 11) [134].

Table 11. NYHA classification system.

	Symptoms
NYHA I	No limitation of ordinary physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath) or anginal pain.
NYHA II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
NYHA III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain
NYHA IV	Severe limitations. Inability to carry on any physical activity without discomfort. Experiences symptoms even at rest. If any physical activity is undertaken discomfort is increased.

NYHA; New York Heart Association. Modified after The Criteria Committee of the New York Heart Association [134].

Quality of life

There is no consensus on the definition of quality of life (QoL) [135]. Life satisfaction is suggested as the most suitable approach to define QoL and Moons *et al* defined quality of life as "the degree of overall life satisfaction that is positively or negatively influenced by an individuals perception of certain aspects of life that are important to them, including matters both related and unrelated to health" [136]. There is a wide range of questionnaires assessing QoL including generic, disease specific or test batteries including both [137]. Two commonly used instruments in Swedish health care are Medical Outcome Study Questionnaire Short Form-36 (SF-36) [138-140] and EuroQoL 5-dimensions (EQ-5D) [141].

The previously reported data on QoL in adults with congenital heart disease are conflicting. Some report that adults with congenital disease had a better QoL than controls, others that it was similar to controls and some that it was worse than in controls. Methodological limitations and differences, such as study population, sample size and evaluation instrument, was suggested to be the reason for these inconsequent findings [135].

When factors associated with QoL was investigated it was found that higher education, higher employment rates, better New York Heart Association (NYHA) functional class, better social support, better exercise capacity and more daily activities were associated with a higher QoL. In contrast, previous

cardiac surgery, having an implantable cardioverter defibrillator (ICD), limited physical functioning and type D (distressed) personality were factors associated with an impaired QoL. Recent studies indicate that sense of coherence is an important predictor of QoL and that this might be a pathway to improvement of QoL [135].

Exercise self-efficacy

Exercise self-efficacy *i.e.* the confidence in being physically active is important for initiation, performance and maintenance of various activities [142]. In children and adolescents with congenital heart disease exercise self-efficacy correlated with physical activity level. Furthermore exercise self-efficacy rather than the severity of the heart lesion *per se* was an important determinant to participate or not in sports and other physical activities. [143]. In adults with congenital heart disease, more symptomatic patients had lower exercise self-efficacy compared to asymptomatic patients. However, no comparison to healthy controls was performed [95].

Rationale for thesis

Thanks to advances in medical and surgical treatments, children with congenital heart disease now have a generally good long-term prognosis and the great majority survive into adulthood [1]. Paediatric patients with congenital heart disease have been extensively investigated with regards to surgical outcomes, cardiac function, growth, development, exercise capacity and physical activity. However the findings of such studies in the paediatric population cannot easily be applied on the adult population with corresponding lesions, due to altered physiological conditions during growth as well as new and previously unknown long-term complications. Moreover, the prevalence of comorbidities, complications (*e.g.* arrhythmias), need for re-intervention and potential need for physiotherapy increases with time and thereby age [11]. The focus of research and care in congenital heart disease must change to better meet the needs of a patient population with a new age distribution. To build upon the successes in paediatric cardiac care, increased knowledge about physical performance, physical activity level, body composition and the effects of exercise training among adults with congenital heart disease is required.

Patients with congenital heart disease generally have reduced exercise capacity compared to their healthy peers. This reduction is less pronounced in patients with simple lesions (*e.g.* valve lesions and shunt lesions) compared to those with more complex lesions. However, there are large variations within each diagnosis group [3, 4]. Many patients reportedly overestimate their exercise capacity [47]. Furthermore, correlations have been found between physical activity level and exercise capacity [94] and between exercise capacity and the sub-component physical functioning of the QoL instrument SF-36 [144]. In patients with complex congenital heart disease reduced muscle function *i.e.* reduced muscle metabolism and lean muscle mass deficit, has been observed which is suggested to negatively affect exercise capacity [45, 79]. Furthermore, reduced muscle function *i.e.* muscle strength and endurance has been reported in adults with various congenital heart lesions [81, 82].

Physical inactivity has emerged as an important cardiovascular risk factor, prompting the WHO to recommend a physically active lifestyle [85-88]. Studies that have assessed physical activity level using accelerometers have reported contradictory results regarding the extent to which physical activity recommendations are reached by adults with congenital heart disease [94, 95]. The usage of an accelerometer provides an estimation of the time spent performing moderate-to-vigorous activity, based on a built-in prediction

equation in which, counts/min is used as a cut-off to determine activity intensity [89, 91]. In individuals for whom cardiac function may be the limiting factor, it could be useful to combine accelerometry with an evaluation method for monitoring the effects of physical activity on heart rate. Thereby a combined accelerometer and heart rate monitor could be used to take both factors into consideration [145, 146].

Physical inactivity and high energy intake are the two most important factors causing overweight/obesity [147]. In the paediatric population of congenital heart disease, an increased prevalence of overweight/obesity has been reported [123-126]. However contradictory results have been reported among adults with corresponding lesions [129, 130]. Furthermore, possible relationships between BMI and specific lesions have not yet been investigated.

Relatively few intervention studies have evaluated the effects of exercise training in adults with congenital heart disease. The existing studies have used a large variety of training modes and the majority have focused on only one diagnosis group [80, 105, 108-117]. Parallels are often drawn between patients with congenital heart disease and patients with congestive heart failure. In the latter group, interval training reportedly increases exercise capacity more than continuous exercise training at a moderate level [103, 104]. Many adults with congenital heart disease are in the middle of life with education, careers and family obligations, and thus a home-based training protocol might be the most suitable. There is a need for increased knowledge regarding home-based exercise training in adults with congenital heart disease.

The aims of the thesis

The general aim of the thesis was to generate increased knowledge on physical performance, physical activity level, body composition and the effects of exercise training among adults with congenital heart disease.

Specific aims of the thesis were to:

- Investigate muscle function in arm, leg and respiratory muscles and reported exercise self-efficacy in adults with different congenital heart lesions and in comparison to healthy age- and sex matched controls.

- Investigate habitual physical activity assessed with a combined accelerometer and heart rate monitor in adults with different congenital heart lesions and in comparison to healthy age- and sex-matched controls.

- Investigate height, weight and body mass index (BMI) in adults with different congenital heart lesions in comparison to the general population using the Swedish registry of Congenital Heart Disease (SWEDCON) and data from the national survey on living conditions (ULF/SILC) performed by Statistics Sweden.

- Investigate height, weight and BMI in relation to diagnosis, NYHA functional class and physical activity level.

- Investigate health related quality of life (EQ-5D) in adults with congenital aortic valve disease and the influence of medical factors, social factors and self-reported level of physical activity on EQ-5D in this population.

- Investigate whether individually adjusted home-based interval training on ergometer cycles can increase the exercise capacity and endurance in adults with complex congenital heart disease.

Materials and methods

Study populations

An overview of study designs, study populations, inclusion and exclusion criteria are presented in Table 12-13. The distribution of different heart lesions in paper I-V and classification of heart lesions into simple or complex lesions is provided in table 14.

Patients

The patients in paper I and II were included from the university hospital centres for adult congenital heart disease in Umeå and Lund. In paper III and IV data on adult patients (≥18 years of age) was extracted from The Swedish Registry on Congenital Heart Disease (SWEDCON). In paper III 40 years of age was chosen as the upper limit for patients with complex lesions as few patients were older. The corresponding upper limit in the group of patients with simple lesions was set to 50 years of age. This was due to a lower number of patients with CoA above 50 years of age compared to the other lesions classified as simple. The patients in study V was recruited via the university hospital centres for adult congenital heart disease in Umeå and Gothenburg. The data presented in paper V only includes patients form the northern health care region.

Controls

The age- and sex-matched controls in paper I and II were randomly recruited via the national population registry. The exclusion criteria for controls were the same criteria as for patients with addition of congenital heart disease (Table 13). In paper III data on height, weight and BMI in controls was extracted from the national living conditions survey (undersökning om levnadsförhållanden, ULF) performed by Statistics Sweden.

Table 12. An overview of study designs and study populations in paper I-V

		Paper I	Paper II	Paper III	Paper IV	Paper V
Study design		cross-sectional	cross-sectional	registry based cross-sectional	registry based cross-sectional	RCT
Patients	n	85	80	2424	315	18
Sex M	n (%)	50 (59)	48 (60)	1403 (58)	224 (71)	9 (50)
F		35 (41)	32 (40)	1021 (42)	91 (29)	9 (50)
Age *years*	mean ±SD	36.8±14.9	37.0±15.3	27.6±5.8 [a] 31.4±8.8[b]	33±10	32.6±14.1
BMI (kg/m²)	mean ±SD	24.3±3.7	24.3±4.2	23.9±4.5[a] 24.6±4.6[b]	24.3±4	25.0±2.6
Pts with simple CHD	n	42	40	1886	315	-
Pts with complex CHD	n	43	40	538	-	18
Controls	n	42	42	4605	-	7*
Sex M	n(%)	26(61.9)	26(61.9)	924(50)[c]	-	2
F		16(38.1)	16(38.1)	921(50)[c] 1344(48.7)[d] 1416(51.3)[d]		5
Age *years*	mean ±SD	36.9±15.0	36.9±15.0	28.3±6.3[c] 33.7±9.3[d]	-	25.7±4.8

BMI; body mass index, Pts; patients, CHD; congenital heart disease, RCT; randomized controlled trial. a) Patients with complex lesions. b) Patients with simple lesions c) controls used in comparison with patients with complex lesions. d) Controls used in comparison with patients with simple lesions *) Patients that were randomised to control group.

Table 13. An overview of inclusion and exclusion criteria in paper I-V.

	Paper I+II	Paper III	Paper IV	Paper V
Inclusion criteria	Age (≥18). Periodic outpatient visit for CHD. Clinically stable condition past 3 months.	Pts palliated with Fontan/TCPC, pts with d-TGA corrected with Senning/Mustard procedure, ToF, PA/DORV and 18-40 years, CoA, ASD, VSD or AS/AR 18-50 years. Available data on height and weight at last clinical visit.	Age (≥18). Main diagnosis unspecified AS, valvular AS or AR, or main diagnosis BAV with previous surgery for AS or AR. Age <50 years at time of initial valve related diagnosis.	Age (≥18). Complex CHD. Clinically stable condition past 3 months.
Exclusion criteria	Intellectual disability or mental illness affecting independent decision making. Extra cardiac-disease affecting physical activity. Other circumstances making participation unsuitable.	CHD associated with genetic syndromes. Heart transplant recipients. Pts with Eisenmenger physiology.	Aortic valve disease associated with Turner or Marfan syndrome. Presence of other important CHD such as previous operation for ToF. Previous intervention for sub-or supra valvular AS. Insufficient data. Diseased at data extraction.	Exercise training ≥2times/week. Arrhythmia at CPET or clinically relevant arrhythmia. Intellectual disability or mental illness affecting independent decision making. Extra cardiac-disease affecting physical activity. Peak VO2 >30 ml/kg/min at run-in CPET. Other circumstances making participation unsuitable.

CHD; congenital heart disease, pts; patients, TCPC; total cavo-pulmonary connection, d-TGA; dextro-transposition of the great arteries; ToF; tetralogy of Fallot, PA; pulmonary atresia, DORV; double outlet right ventricle, CoA; coarctation of the aorta, ASD; atrial septal defect, VSD; ventricular septal defect, AS; aortic stenosis; AR; aortic regurgitation, BAV; bicuspid aortic valve, CPET; cardiopulmonary exercise test.

Table 14. An overview of distribution and classification of heart lesions in paper I-V.

	Paper I	Paper II	Paper III	Paper IV	Paper V
Simple lesions:	n=42	n=40	n=1886	n=315	n=0
CoA	12	12	414		
AS	3	3	561#	315#	
AR	3	3	#	#	
AS/AR	4	4	#	#	
VSD	15	14	497		
ASD	2	1	414		
PFO	1	1			
PDA	1	1			
MR	1	1			
Complex lesions:	n=43	n=40	n=538	n=0	n=18
d-TGA	5	5	122		5
ccTGA	2	2			2
ToF	9	8	238		3
PA/DORV	5	5	81		1
DILV (no intervention)	1	1			
Fontan/ TCPC*	11	9	97		5
Ebstein	3	3			
Eisenmenger	6	6			
Miscellaneous	1	1			1
Complete AV-septal defect					1

Distribution of heart lesions and classification into simple or complex lesion. CoA; coarctation of the aorta, AS; aortic stenosis, AR; aortic regurgitation, VSD; ventricular septal defect, ASD; atrial septal defect, PFO; persistent foramen ovale, PDA; persistent ductus arteriosus, MR; mitral regurgitation, d-TGA; dextro-transposition of the great arteries, ccTGA; congenitally corrected transposition of the great arteries, ToF; tetralogy of Fallot, PA; pulmonary atresia, DORV; double outlet of right ventricle, TCPC; total cavo-pulmonary connection, DILV; double inlet left ventricle. *) Patients palliated for tricuspid atresia, PA or DILV. #) no further subdivision into AS, AR or AS/AR were made.

Databases and registries

The SWEDCON registry

The Swedish Registry on Congenital Heart Disease (SWEDCON, www.ucr.uu.se/swedcon) was started in 1998 and covers the seven health care regions of Sweden and contains data on approximately 11.300 adults, defined as ≥16 years old (2014). Data on age, sex, diagnosis, interventions, medication, NYHA-class, symptoms, smoking habits, blood pressure, ECG, echocardiography, arterial oxygen saturation, EQ-5D and self-reported level of physical exercise is registered by each of the seven GUCH-centres on each clinical visit/test. The variable self-reported level of exercise was defined as sports/exercise performed more or less for its own sake. To walk to or from work or school was not considered as sports/exercise. The estimated dose per week was classified into three categories: none, <3hrs/w, >3hrs/w. The patients were instructed to choose the category that best described their level of activity. Data was extracted on two different occasions 2009-01-15 (paper IV) and 2013-02-17 (paper III). The data obtained from the last available clinical visit or test was used in respective analyses (paper III, IV).

ULF/SILC data

On behalf of the Swedish parliament, the national living conditions survey (ULF) has been performed regularly by Statistics Sweden since 1975. In 2008 it was integrated with the European Union Statistics on Income and Living Conditions (SILC). Yearly telephone interviews are performed in 12.000-13.000 randomly selected adult (≥16 years of age) individuals. The interviews cover housing, health, employment, civic activities etc. (paper III).

Methods of measurements

An overview of outcome measures analysed in paper I-V is presented in Table 15.

Table 15. An overview of outcome measures analysed in paper I-V.

	Paper I	Paper II	Paper III	Paper IV	Paper V
Muscle function					
Shoulder flexion	x				
Heel lift	x				
MIP/MEP	x				
Physical activity					
Actiheart data		x			
Body composition					
Height			x		
Weight			x		
BMI			x		
Exercise capacity					
Peak VO_2					x
Peak work load					x
Endurance time					x
Questionnaires					
ESES	x				
EQ-5D				x	

MIP; maximum inspiratory pressure, MEP; maximum expiratory pressure, BMI; body mass index, ESES; exercise self-efficacy scale, EQ-5D, EuroQoL 5-dimensions.

Muscle function tests

The muscle function tests were performed using standardized instructions. The patients were instructed to perform the tests to a maximum effort, but no additional encouragement was used during the tests. The unilateral isotonic shoulder flexion test and heel-lift test evaluates muscle endurance. These tests were first developed and evaluated in patients with congestive heart failure. Furthermore these tests have good test-retest reliability [148]. In addition these tests have been also used to evaluate muscle function in adults with congenital heart disease [82].

Unilateral isotonic shoulder flexion

The test was performed with the test person sitting with the back against the wall and a weight (women 2kg and men 3kg) held in the hand of the dominant side. The person was asked to elevate the arm, from 0° to 90° flexion, as many times as possible with a frequency of 20 contractions per minute following a metronome (KORG metronome MA-30, KORG Inc., Japan). The test was discontinued when the subject was unable to elevate the arm up to 90° or to sustain the frequency. The number of repetitions was noted (paper I) [148].

Heel-lift

The test was performed with the test person standing on one leg on a 10° tilted wedge. A light support by the hands towards the wall for balance was allowed. The contralateral foot was to be held slightly above the floor and the knee of the tested leg to be kept straight. The person was instructed to perform as many heel-lifts as possible with a frequency of 30 repetitions every minute following a metronome (KORG metronome MA-30, KORG Inc., Japan). A measuring stick was used to individually define the height of a maximum heel-lift prior to the test. Then the patient was instructed to touch the stick with their head on every heel-lift. The test was discontinued when the subject was unable to touch the stick or to keep the frequency. The number of repetitions was noted (paper I) [148].

Respiratory muscle function

Maximum inspiratory pressure and maximum expiratory pressure (MIP/MEP) are indirect measures of respiratory muscle strength [149]. MIP/MEP has previously been evaluated in adults with congenital heart disease [81]. The hand-held respiratory pressure meter (Micro RPM™, Care Fusion, San Diego, CA, USA) was used to evaluate MIP/MEP. Micro RPM™ was previously validated on healthy subjects [150]. The test was performed with the test person sitting on a chair. A soft nose clip was worn during the test to prevent nasal inhalation/exhalation. To measure MIP the test person first performed a maximum exhalation, then the pressure meter was put into the mouth and a maximum inhalation was performed. MEP was measured during a maximum exhalation that followed a maximum inhalation. The highest pressure achieved, cm H_2O, in one out of three tests was registered (paper I) [150].

Monitoring of physical activity

The physical activity level was assessed using a combined accelerometer and heart rate monitor, Actiheart (CamNTech Ltd., Cambridge, UK) described in detail elsewhere [145]. The Actiheart monitor was applied using Red Dot 2560 ECG electrodes (3M, St Paul, MN, USA). The site for application of the monitor was on the left side of the chest at heart level. Furthermore, the 30-second epoch was used as frequency for data storage. The monitor was to be worn 24 hours per day during four consecutive days and only to be removed during water immersion such as swimming or taking a bath. The participants were instructed to continue with their habitual daily activities and to document electrode changes and removal of the Actiheart monitor. During initialisation of the recording period the participant performed a submaximal step-up test according to a standardized procedure. The instruction was to step up-and down a 20 cm high step-box while keeping a guided step-rate. The step-rate was ramped from an initial rate of 15 steps per min to 33 steps per minute. The entire test lasted 8 minutes and was followed by two minutes rest sitting on a chair [151, 152]. The test was interrupted if the participant rated their perceived exertion ≥17 (very hard) according to the Borg Rating of Perceived Exertion scale [153]. The Actiheart monitor was worn during the entire step-test and the results of the test were used as a reference when analysing habitual physical activities.

The data recorded with Actiheart was analysed regarding accelerometer counts per day as a measure of total volume of physical activity and time spent at moderate-to-vigorous physical activity. Furthermore, the extent to which the current recommendations on physical activity were met was analysed. All analyses were adjusted for wear time. Two different models, based on heart rate data, were used to estimate time spent at moderate-to-vigorous physical activity. In one of the models 1.75 x resting heart rate was calculated and used as cut-off [154]. Resting heart rate was defined as the heart rate ranked as the 30th lowest heart rate in 24 hrs. In the second model the individual HR at 3 minutes into the step-test was used as cut-off value.

Exercise capacity

Cardiopulmonary exercise tests

The cardiopulmonary exercise tests were performed on an ergometer cycle (Rodby RE990, Rodby Innovation, Vänge, Sweden) and a Jaeger Oxycon Pro (CareFusion, GmbH, Hoechberg, Germany) was used for breath-by-breath analysis of respiratory gases during exercise.

Incremental cardiopulmonary exercise test

Incremental cardiopulmonary exercise testing (CPET) is considered the "gold standard" method used to evaluate exercise capacity [118]. The test was performed according to a standardized protocol starting with a 3 min reference cycling, followed by an increment of workload every minute. The size of increment (10, 15, 20 W) was calculated from height, weight and "fitness" level. The test was performed with a standardized pedal rate of ≈60 rpm and the standard test termination criteria were used [42, 118, 119]. To ensure standardization, the patients were instructed that rating ≥17 (very hard) on the Borg RPE scale [153] should correspond to a perceived exertion of "not coping yet another increase of workload". After test termination, a recovery period of 3 min sitting on the ergometer cycle followed. Peak VO_2 (ml/kg/min), peak workload (W), peak heart rate and respiratory exchange ratio (RER) were analysed (paper V) [42, 118, 119].

Constant work rate cardiopulmonary exercise test

Constant work rate CPET is an established method used to evaluate endurance exercise capacity pre and post pulmonary rehabilitation program in patients with chronic obstructive pulmonary disease (COPD) [155]. The test is usually performed at 75-80% of peak work load achieved during a former incremental CPET [155, 156]. In patients with COPD the constant work rate CPET is the most responsive test when evaluating the effects of exercise training or medical treatment [157]. This test has not previously been used in the population of adults with congenital heart disease. The constant work rate CPET was performed at 75% of peak work load achieved at the initial incremental CPET. The main outcome variable analysed was test duration (min) (paper V).

Body mass index

Data on height, weight, BMI, age and gender was extracted from the SWEDCON registry and ULF/SILC database (paper III). In paper III height, weight and BMI were the primary outcome measures analysed. In the other papers the corresponding data was used as descriptive data of the study population. The WHO classifications regarding underweight (BMI≤18.5), overweight (BMI≥25) and obesity (BMI≥30) were applied [120]. Moreover, when analysed as a dependent variable in regression analysis BMI was used in its continuous form (paper III).

Questionnaires and functional class

EQ-5D

The EQ-5D is a quality of life (QoL) questionnaire, developed by the Euro-QoL group [141]. EQ-5D is also one of the variables included in the SWEDCON registry and was analysed in paper IV. The questionnaire consists of the 5 dimensions (EQ-5D self-classifier); mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is graded into three levels; (1) no problem, (2) some or moderate problems and (3) extreme problems. This gives 243 possible health states [141]. The results of EQ-5D were converted into a single summary index ($EQ\text{-}5D_{index}$) by applying a formula weighting all levels in all five dimensions [158]. To perform this calculation the British index tariff was used. [159]. This tariff is also commonly used by the National Board of Health and Welfare, Sweden [160]. An $EQ\text{-}5D_{index}$ score of one indicates best possible health state whereas a score of zero represents the worst possible health status or death. It is possible to achieve a value below zero using this tariff, but when this occurs it is often replaced with a value zero [158]. The EQ-5D has been used in previous reports on health related QoL in adults with congenital heart disease [161, 162].

The exercise self-efficacy scale

The exercise self-efficacy scale was used to evaluate the attitude towards exercise training and the confidence to persist to exercise despite different barriers (paper I). The questionnaire consists of ten items, on a four-point Likert scale, and the score range from 10 to 40, where 40 denote the best possible exercise self-efficacy [163]. The Swedish version of exercise self-efficacy scale has recently been validated in patients with neurological diseases [164]. Moreover, it has been used in evaluation of an exercise training protocol in patients with chronic obstructive pulmonary disease [165]. Exercise self-efficacy has previously been evaluated in children and adults with congenital heart disease with similar instruments [95, 143, 166].

NYHA class

The New York Heart Association (NYHA) classification system [134] was used in order to describe the study population in paper I-IV.

Physiotherapy intervention

Paper V was a two-armed randomised clinical trial including patients with complex congenital heart diseases. Methods of outcome measurements were incremental CPET and constant work rate CPET (previously described).

The randomization process

The randomization into intervention or control group in a ratio 2:1 was performed using computer generated block randomization and processed by a person independent of recruitment and outcome assessment. The allocation sequence was kept in an opaque, sealed and stapled envelope and was not revealed to the patient or physiotherapist until the run-in tests were completed. The outcome assessors were kept blinded to the group allocation. The patients were repeatedly instructed not to reveal their group allocation to the outcome assessors during the follow-up tests. The controls were instructed to continue with their daily activities.

Exercise training protocol

The intervention protocol consisted of an individually adjusted home-based interval training protocol on an ergometer cycle with manually adjusted braking system (Tunturi®T 20 /Tunturi®, Tunturi- Hellberg Oy Ltd, Åbo; Finland or Bremshey BF3, Escalade Int. Ltd, UK) (paper V). The exercise training was performed 3 times per week during twelve consecutive weeks. Individual training heart rate range corresponding to 75-80% of peak VO_2 ($THR_{75\text{-}80\%}$) using the Karvonen method was used as exercise intensity [101]. During the initial two weeks, the protocol consisted of three intervals at $THR_{75\text{-}80\%}$ separated by a 3 min active recovery pedalling with only light load or without load. The following weeks a fourth interval at $THR_{75\text{-}80\%}$ was added. The maximum interval duration at $THR_{75\text{-}80\%}$ was 5 min. If the maximum test duration at constant work rate CPET was ≤5 min the interval at THR 75-80% was calculated as test duration minus 1 minute (protocols are presented in Appendix). In order to monitor the training heart rate the patients wore a heart rate monitor (Polar RS 300X, Polar Electro Oy, Kempele, Finland). The heart rate data was regularly transferred to a web page where both the patient and physiotherapist had access. The physiotherapist also had a weekly contact with the patients to enable progress in training, feedback and to support compliance. In case of disruption of the training period due to *e.g*. infection or travel the period was extended with the same amount of time. Thirty-six exercise training sessions were the total possible number sessions if the intervention protocol was

followed fully. Furthermore, twenty-eight (78%) sessions was set as a goal for minimum number of completed sessions.

Statistics

The Statistical Package for the Social Sciences, SPSS version 18, 20, 22 (IBM, Armonk, NY, US) was used in the statistical analyses (paper I-V). Clinical data was presented as means ± 1 standard deviation (SD), as median with range (min-max) or interquartile range (IQR) or as ratios. The differences in means, medians and ratios were analysed using one-way ANOVA, Kruskal-Wallis test or multi frequency cross-tables if three or more groups. Students *t*-test, Mann-Whitney *U*-test or chi-square test was used in *post-hoc* analyses or when comparing two groups. The Bonferroni correction was applied to correct for multiple comparisons. The null hypothesis was rejected for $p \leq 0.05$.

To evaluate the effects of different independent variables on the dependent variable, regression analyses were used. Linear regression was used in paper I and III. In paper IV the outcome variable EQ-5D was dichotomised into $\text{EQ-5D}_{\text{index}}=1$ and $\text{EQ-5D}_{\text{index}}<1$ since the majority of patients (64.1%) rated their health state as $\text{EQ-5D}_{\text{index}}=1$. Therefore, logistic regression was used with the dichotomized $\text{EQ-5D}_{\text{index}}$ as dependent variable. In paper II the Poisson regression, with log link function, was used as appropriate when the unit of the dependent variable was counts and with a Poisson distribution. Furthermore, we used monitor wear time as offset variable, to adjust for wear time. The univariate regression was followed by a multivariate regression model analysis, where variables from the univariate regression analyses with $p \leq 0.15$ or of principal interest (*e.g.* age, sex*)* were selected. The multivariate regression models were run in a manual backward mode and correlations and multi-collinearity were assessed during the analysis. Results of linear and Poisson regression analyses were presented using B, which denotes the effect of the independent variable on the dependent variable, with a corresponding 95% confidence interval (CI) and *p*-value. Results of logistic regression analysis were presented with odds ratio (OR) with corresponding 95% CI and *p*-value.

In paper IV the variables from the two multivariate models (full and restraint) were extracted and reapplied on the cohort order to analyse their explanatory strength. Furthermore, their accuracy was evaluated with receiver operating curved analysis (paper IV).

Intention-to-treat analysis was applied in paper V, *i.e.* all randomised patients that were followed-up were included in analysis, even those that did not follow the intervention protocol.

Results

Muscle function (paper I)

Skeletal muscle function measured as muscle endurance in shoulder- and calf muscles was lower in adults with complex congenital heart lesions in comparison to patients with simple lesions as well as age- and sex- matched controls. In addition, MIP was reduced in patients with complex as well as simple lesion in comparison to controls. MEP was only impaired in those with complex lesions when compared to controls (Table 16).

Table 16. Results of muscle function tests and rating of exercise self-efficacy.

		Complex lesions (n= 43)	Simple lesions (n=42)	Controls (n=42)	*p-value*
Shoulder flexions *(reps)*	mean±SD	28.2±11.1	54.9±24.9	63.6±40.4	**≤0.001[a]** **≤0.001[b]** 0.49[c]
Heel-lifts *(reps)*	mean±SD	17.6±7.7	23.2±7.0	26.3±12.8	**≤0.024[a]** **≤0.001[b]** 0.43[c]
MIP *(cmH_2O)*	mean±SD	80.7±26.7	94.1±30.0	111.1±29.9	0.10[a] **≤0.001[b]** **0.023[c]**
MEP *(cmH_2O)*	mean±SD	110.8±39.9	126.4±34.3	141.8±39.5	0.18[a] **≤0.001[b]** 0.20[c]
ESE *(score)*	mean±SD	28.0±8.3	31.6±5.9	33.4±6.1	0.62[a] **0.002[b]** 0.19[c]

SD; standard deviation, reps; number of repetitions MIP; maximum inspiratory pressure, MEP; maximum expiratory pressure, ESE; exercise self-efficacy. a) Comparison between patients with complex lesion and patients with simple lesions. b) Comparison between patients with complex lesions and controls. c) Comparison between patients with simple lesions and controls. Analyses were performed using one-way ANOVA and Bonferroni correction for multiple comparisons were applied.

Factors associated with reduced muscle function

In a multivariate linear regression model the complexity of the heart lesion together with a lower exercise self-efficacy score were associated with an impaired shoulder muscle function in adults with congenital heart lesion (Complexity of heart lesion; B=-24.1 95% CI-32.0 - -16.2, $p \leq 0.001$, exercise self-efficacy score; B= 0.7 95%CI 0.16-1.23, $p=0.011$). Moreover, complexity of the heart lesion and female sex were associated with a reduced calf muscle function (Complexity of heart lesion; B=-5.6 95%CI -8.7 - -2.7, $p \leq 0.001$, female sex; B=-3.4 95%CI -6.5 - -0.3, $p=0.03$).

Exercise self-efficacy (paper I)

Patients with complex lesions rated their exercise self-efficacy lower than controls, while no differences were found in comparison to patients with simple lesions (Table 16).

Physical activity (paper II)

Time spent at moderate-to-vigorous physical activity level

There was no difference in time spent at moderate-to-vigorous physical activity level between patients with simple lesions, complex lesions and controls expressed as percentage of time spent with a heart rate ≥1.75 x resting HR (median percent wear time, interquartile range [IQR], simple lesions; 13.8 % [6.7-21.3], complex lesions; 13.6% [5.3-18.5], controls 11.1% [6.8-23.5], $p=0.82$). Furthermore, the same result was found when time spent with a heart rate ≥ the individual 3 min step test HR (median percent wear time [IQR] simple lesions; 1.7% [0.7-4.3], complex lesions; 1.0% [0.3-2.7], controls; 1.9% [0.9-4.5], $p=0.17$). Data also showed that male patients were more active at a moderate-to-vigorous level in comparison to the female patients when analysing time ≥ the individual 3 min step heart rate (median percent wear time [IQR], men; 1.6%[0.7-4.3] *vs.* women; 0.8%[0.05-2.5], $p=0.042$).

Sedentary time

No differences between patients and controls were found regarding sedentary time (median percent wear time [IQR], simple lesions; 67.2% [53.6-78.4], complex lesions; 63.6% [53.6-79.5], controls; 64.9% [53.6-77.3], $p=0.99$).

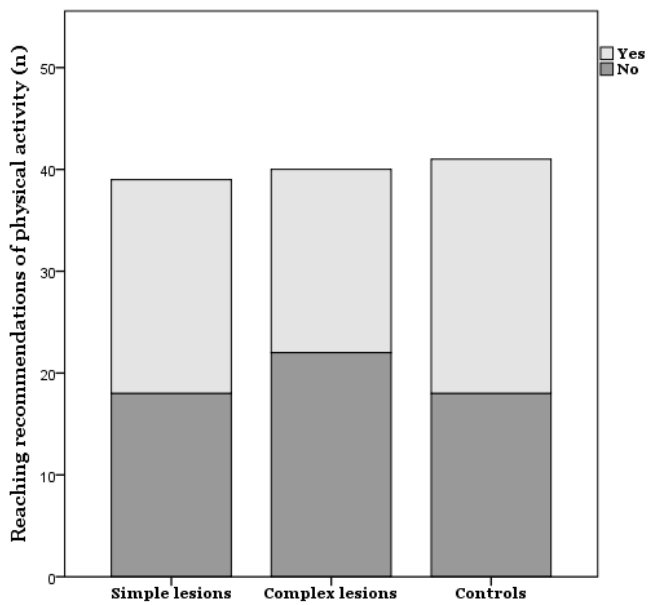
Accelerometer counts per day

Patients with simple lesions had a higher accelerometer count/day adjusted for wear time in comparison to both patients with complex lesions and controls (median x 1000 counts per day [IQR], simple lesions; 107.7 [76.3-139.1] *vs.* complex lesions 72.8 [49.2-101.0], $p \leq 0.001$ and simple lesions; 107.7 [76.3-139.1] *vs.* controls 78.3 [58.7-106.9], $p=0.002$).

Reaching recommendations of physical activity

The current recommendations on physical activity, 21.4 min/day at moderate-to-vigorous level, was not reached by 18 patients (46%) with simple lesions, 22 patients (55%) with complex lesions and 18 (44%) of the controls (Figure 5). There were no differences between the groups.

Figure 5



Distribution of patients with simple lesions, complex lesions and controls reaching (yes) respectively not reaching (no) the WHO recommendations of physical activity.

NYHA class

When analysing time spent at moderate-to-vigorous physical activity, defined as a heart rate ≥1.75 x resting heart rate, patients in NYHA class II and III grouped together were less active compared to patients in NYHA class I but no difference compared to controls was found. No differences between the groups were found when corresponding analyses were made using time spent ≥ 3min step test HR. Regarding accelerometer counts per day patients in NYHA class I had more accelerometer counts per day both in comparison to patients in NYHA II+III and controls. Furthermore controls had more accelerometer counts compared to patients in NYHA class II+III (Table 17).

Table 17. Comparison of physical activity level between patients in NYHA class I, NYHA class II+III and controls.

	NYHA I	**NYHA II+III**	**Controls**	***p-value***	***Post hoc***
MVPA time (% wear time):					
Time ≥ 1.75 x resting HR	15.8 (9.0-21.0)	7.2 (1.9-15.2)	11.1 (6.8-23.5)	**0.018**[a]	**0.012**[b] 0.99[c] 0.22[d]
Time ≥ 3 min step-test HR	1.5 (0.4-4.1)	0.9 (0.3-2.7)	1.9 (0.9-4.5)	0.35[a]	
Accelerometry (x 1000 counts per day)	103.3 (77.4-130.4)	53.8 (44.0-68.2)	78.3 (58.7-106.9)	**≤0.001**[a]	**≤0.001**[b] **0.006**[c] **0.018**[d]

Statistics presented as medians (interquartile range). MVPA; moderate to vigorous physical activity, HR; heart rate. a) Denotes comparison between the patients in NYHA class I, NYHA class II+III and controls using Kruskal-Wallis test. b) Denotes comparison between patients in NYHA I and NYHA II+III. c) Denotes comparison between NYHA I and controls. d) Denotes comparison between patient in NYHA class II+III and controls. In b-d analysis with Mann-Whitney *U* test was performed and Bonferroni corrections were applied.

Factors associated with physical activity

Factors independently associated with time spent at ≥ 3 min step test heart rate are presented in Table 18 and factors associated with accelerometer count per day are presented in Table 19.

Table 18. Results of final Poisson regression model with percent wear time spent at ≥ 3 min step test heart rate.

	B	**95%CI (min-max)**	***p*-value**
Sex			
female *(ref)*	0		
male	0.8	0.72-0.88	≤0.001
NYHA class			
I *(ref)*	0		
II	-0.75	-0.9- -0.61	≤0.001
III	1.02	0.92-1.11	≤0.001
Age *years*	-0.058	-0.06 - -0.05	≤0.001

B; the effect of the independent variables on the dependent variable, CI; confidence interval, ref; reference.

Table 19. Results of final Poisson regression model with accelerometer counts per day as dependent variable.

	B	**95%CI (min-max)**	***p*-value**
Sex			
female *(ref)*	0		
male	-0.082	-0.083 - -0.08	≤0.001
NYHA class			
I *(ref)*	0		
II	-0.027	-0.029 - -0.025	≤0.001
III	-0.73	-0.74 - -0.73	≤0.001
Age *years*	-0.01	-0.01 - -0.01	≤0.001
Beta-blockers			
no *(ref)*	0		
yes	-0.011	-0.013 - -0.009	≤0.001

B; the effect of the independent variables on the dependent variable, CI; confidence interval, ref; reference.

Body Mass Index (BMI) (paper III)

Prevalence of underweight and overweight/obesity

The prevalence of underweight (BMI≤18.5) was higher in men with congenital heart disease in comparison to the general population (complex lesions; n=16, 4.9% *vs.* controls; n=8, 0.9%, $p \leq 0.001$ and simple lesions; n=34, 3.2% *vs.* controls n=8, 0.6%, $p \leq 0.001$). Furthermore, in men palliated with Fontan/TCPC procedure, PA/DORV, and aortic valve disease the prevalence of overweight/obesity (BMI≥25) was lower than in the general population (Table 20). In women, no differences regarding underweight were found in comparison to the population. However, a higher prevalence of overt obesity (BMI>30) was found in women with simple lesions in comparison to population data (simple lesions; n=104, 12.8% *vs.* controls; n=128, 9.0%, $p=0.005$). A subgroup analysis showed that only women with aortic valve disease differed regarding obesity (AS/AR; n=25, 16.3% *vs.* controls; n=128, 9.0%, $p=0.02$).

Height and BMI

Men with complex lesions were shorter compared to controls (Fontan/TCPC; 177.1±6.2 cm, atrial switch; 178.9±5.8 ToF; 177.6±7.4 cm PA/DORV; 176.5±7.8 cm, *vs.* controls; 181.0±6.8cm, $p \leq 0.001$, $p=0.036$, $p \leq 0.001$, $p \leq 0.001$). Shorter stature was also found in men with VSD (VSD; 178.9±7.7 cm *vs.* controls; 180.7±6.8 cm, $p \leq 0.001$). In addition those palliated with Fontan/TCPC procedure and PA/DORV had lower BMI when compared to control data (Fontan/TCPC; 22.4±2.7, PA/DORV; 22.7±3.5, *vs.* controls; 24.9±3.6, $p \leq 0.001$, $p \leq 0.001$,). Furthermore, men with VSD and ASD had lower BMI than controls (VSD; 24.7±4.3, ASD; 24.6±4.3 *vs.* controls; 25.4±3.8, $p=0.048$ and $p \leq 0.001$). In women with congenital heart disease patients with ToF, VSD and AS/AR had a shorter stature in comparison to controls (ToF; 163.6±8.4 cm *vs.* controls; 166.7±6.6 cm, $p=0.006$ and VSD; 165.2±7.1 cm *vs.* controls; 166.6±6.6, $p=0.012$, AS/AR; 164.2±8.1 *vs.* controls; 166.6±6.6 cm, $p \leq 0.001$). No further differences regarding height and BMI were found.

Effects of previous intervention

The ANOVA showed no effects of previous surgical intervention on BMI among patients with simple lesions. In the corresponding analysis regarding height, patients (men and women) with previous intervention for ASD and

male patients operated for VSD were shorter compared to those without previous intervention (ASD with previous intervention; 169.8±10.5 cm *vs*. no intervention; 172.7±10.0 cm p=0.048 and male patients with previous intervention for VSD; 176.5±8.9 cm *vs*. no intervention; 180.0±6.7 cm, p=0.012). No further differences regarding effects of previous intervention height were detected.

Factors associated with BMI

Factors associated with BMI in adults with complex lesions and simple lesions are presented in Table 21 and Table 22 respectively.

Table 20. Prevalence of overweight/obesity (BMI >25) in men and women with complex and simple lesions.

Complex lesions		**Controls**	**Fontan/TCPC**	***p***	**Atrial switch**	***p***	**ToF**	***p***	**DORV/PA**	***p***
		(n=924)	(n=53)		(n=84)		(n=150)		(n=41)	
Men										
BMI ≥25	n (%)	397(43.0)	8(15.1)	**≤0.001**	33(39.3)	0.99	57(38.0)	0.99	9(22.0)	**0.048**
Women		(n=921)	(n=44)		(n=38)		(n=88)		(n=40)	
BMI ≥25	n (%)	222(24.1)	6(13.6)	0.66	14(36.8)	0.45	31(35.2)	0.13	19(25.0)	0.99
Simple lesions		**Controls**	**CoA**	***p***	**VSD**	***p***	**ASD**	***p***	**AS/AR**	***p***
		(n=1344)	(n=261)		(n=253)		(n=153)		(n=408)	
Men										
BMI ≥25	n(%)	662(49.3)	109(41.8)	0.16	105(41.5)	0.14	64(41.8)	0.99	153(37.5)	**≤0.001**
Women		(n=1416)	(n=153)		(n=244)		(n=261)		(n=153)	
BMI≥25	n(%)	456(32.2)	46(30.1)	0.99	75(30.7)	0.99	103(39.5)	0.13	54(35.3)	0.99

BMI; body mass index, n; number, TCPC; total cavo-pulmonary connection, ToF; tetralogy of Fallot, DORV; double outlet right ventricle; PA; pulmonary atresia, CoA; coarctatio aortae, VSD; ventricular septal defect, ASD; atrial septal defect, AS; aortic stenosis, AR; aortic regurgitation. Bonferroni correction was applied to correct for multiple comparison.

Table 21. Results of the final linear regression model regarding adults with complex congenital heart disease with BMI as dependent variable.

	B	**95% CI (min-max)**	***p*-value**
Age *years*	0.14	0.08-0.21	≤0.001
Cardiovascular medication			
no *(ref)*	0		
yes	-0.98	-1.76 - -0.20	0.013

B; the effect of the independent variables on the dependent variable, CI; confidence interval, ref; reference.

Table 22. Results of the final linear regression model regarding adults with simple congenital heart disease with BMI as dependent variable.

	B	**95% CI (min-max)**	***p*-value**
Age *years*	0.092	0.07-0.12	≤0.001
NYHA			
I (*ref*)	0		
II	1.68	0.71-2.64	≤0.001
III	3.18	0.61-5.75	0.015
Cardiovascular medication			
no (*ref*)	0		
yes	0.65	0.09-1.2	0.023
Physical exercise)			
none (*ref*)	0		
<3h/w	-0.6	-1.12 - -0.08	0.025
>3h/w	-1.2	-1.76 - - 0.65	≤0.001
Sex			
men (*ref*)	0		
women	-0.7	-1.15 - - 0.25	0.002

B; the effect of the independent variables on the dependent variable, CI; confidence interval, h/w; hours per week, ref; reference.

Health related quality of life (EQ-5D) (paper IV)

The majority of patients with aortic valve disease (n=202, 64.1 %) rated their health related QoL as best possible ($EQ\text{-}5D_{index}=1$) and 113 (35.9%) reported some impairment of health related QoL ($EQ\text{-}5D_{index}<1$) with a mean $EQ\text{-}5D_{index}$ 0.73±0.17.

Factors associated with EQ-5D

In the final multivariate logistic regression model physical exercise >3h/w was associated with best possible health related QoL ($EQ\text{-}5D_{index}=1$) (exercise >3h/w; OR=0.36 95%CI 0.16-0.81, p=0.013). On the other hand, the presence of cardiovascular symptoms, active smoking, previous valve surgery, lower educational level and a higher systolic blood pressure was associated with impaired health related QoL ($EQ\text{-}5D_{index}<1$) (symptoms; OR=9.79 95%CI 3.51-27.32, $p\leq0.001$, active smoking; OR= 4.72 95%CI 1.81-12.34, p=0.002 valve surgery; OR=1.99 95%CI 1.13-3.5, p=0.017, low educational level; OR=3.12 95% 1.18-8.29, p=0.022, systolic blood pressure; OR=1.02 95%CI 1.00-1.04, p=0.029).

Effects of physiotherapy intervention (paper V)

Of the 19 patients (9 women) included in the study 12 were randomised to intervention and 7 as controls. One patient was excluded due to palpitations during exercise training. Eighteen patients were analysed after follow-up.

Exercise capacity

Peak VO_2 at incremental CPET increased in the intervention group (14%) but not in comparison to the controls (5%) (median [range]; 4.7 [-1.3-7.2] ml/kg/min *vs.* 1.8 [-3.3-5.1] ml/kg/min, p=0.18). The median peak workload at incremental CPET increased in the intervention group (18%) compared to controls (0.3%) (20 [-10-70] W *vs.* 0 [-10-15] W, p=0.01). Furthermore, the median test duration at constant work rate CPET increased (133%) in the intervention group compared to the controls (1%) (12 [-4-52] min *vs.* 0 [-4-2] min, p=0.003).

Compliance

The number of registered exercise sessions ranged from 17-36, thus the compliance to the intervention protocol was in mean 81%±16.

Sex differences (paper I, II, III)

Regarding muscle function male patients performed more heel-lifts and higher MIP/MEP compared to the female patients (heel-lifts; n=21.7±8.5 *vs.* n=18.4±6.2, p=0.045, MIP; 94.7±30.4 cmH_2O *vs.* 76.7±23.5 cmH_2O, p=0.004, MEP; 134.9±36.6 cmH_2O, *vs.* 95.1±25.3 cmH_2O, $p \leq 0.001$). No difference in number of shoulder flexions was found (paper I). Furthermore, it was found that male patients spent more time at moderate-to-vigorous physical activity compared to the females (paper II). As previously presented, a higher prevalence of underweight together with a lower prevalence of overweight/obesity was found in men with congenital heart disease compared to population data. Differences were also found regarding height especially in those with complex lesions, while only limited differences were found in women (paper III).

Missing-data analysis (paper II, III, IV)

Missing data analysis was conducted in the subjects that declined participation or did not appear at clinical visit in paper II. No differences regarding age, sex or complexity of lesion was found in comparison to study participants. Missing data analysis was also conducted on data from Paper III regarding patients with missing data on height or weight with complex or simple congenital heart lesions included for analysis of BMI. No differences regarding height were found between patients with missing data on weight compared to those with complete data on height and weight. Finally missing-data analysis was applied on data from paper IV regarding patients with missing EQ-5D data. The analysis showed that patients with missing EQ-5D data were slightly older (35.4±12.0 years *vs.* 32.0±10.3 years, p<0.001). This was probably because the EQ-5D was not used as a variable in SWEDCON until 2005, with some additional delay before the instrument was established in clinic. No other differences were detected.

Discussion

The results of this thesis showed that adults with complex congenital heart disease had impaired muscle function in comparison to age- and sex-matched controls. Furthermore, a higher prevalence of underweight and lower prevalence of overweight/obesity was found in men. Additionally, men with complex lesions had shorter stature compared to controls. The differences in women with congenital heart disease were however less pronounced. Moreover, adults with congenital heart disease were physically active to same extent as the controls at a moderate-to-vigorous activity level. It was also found that approximately half of both of patients and controls were insufficiently active according to the current recommendations on physical activity. In addition, a higher physical activity level *i.e.* exercise training ≥3h/w was associated with a better QoL among adults with congenital aortic valve disease. In contrast, cardiovascular symptoms, previous valve surgery, active smoking, lower educational level and a higher systolic blood pressure were associated with impaired QoL. The intervention study showed that interval training increased the peak aerobic capacity as well as endurance capacity in adults with complex congenital heart disease.

Muscle function

The generalised impairment of muscle function found in adults with complex congenital heart disease is probably due to multiple factors. In our analysis, complexity of lesion emerged as the most important factor. Complexity of the lesion is a variable related to several other factors which are potential confounders *e.g.* on-going cardiovascular medication, previous interventions [16], impaired pulmonary function [70], overprotection by parents and relatives, imprecise advice regarding physical activity and exercise training from healthcare providers [167, 168] and current NYHA-class [169].

Impaired muscle function evaluated with shoulder flexion test and heel-lift test was previously reported in adults with congenital heart lesions. However, the control population was substantially older [82] than in the present thesis which might provide an overestimation of the muscle function in the patients.

Consistent with the results of the present thesis, impaired MIP/MEP in adults with complex congenital heart lesions was observed by others. They also found a correlation between impaired respiratory muscle function and exercise capacity [81]. Moreover, abnormal pulmonary function is relatively common in adults with congenital heart disease, especially in patients with

complex lesions. Previous thoracotomy, presence of scoliosis and palsy of the diaphragm are important factors that may lead to restrictive pulmonary function [66]. Greutmann *et al.* proposed that impaired respiratory muscle function contributes to the reduced dynamic lung capacity (FEV1 and FVC) found in this patient population and is thereby possible to target with respiratory muscle training [81]. In adults with congestive heart failure, inspiratory muscle training was reported to have positive effects on exercise capacity [170].

The cause of the impaired muscle function is unknown but reduced muscle mass might be one contributing factor. In patients with congestive heart failure muscle wasting is a common co-morbidity [74, 75]. Reduced skeletal muscle mass and abnormal muscle metabolism has been reported in adults palliated with Fontan procedure. In addition, reduced muscle mass was associated with reduced aerobic exercise capacity [79]. A lean mass deficit was also observed in children and adolescents with the corresponding lesions [171]. These results indicate that myopathy might be present in adults with congenital heart disease corresponding to what has been observed in patients with congestive heart failure [74, 78]. However, in congenital heart disease the impact on muscle function by the heart lesion might be milder but is present over a longer period of time. Reduced muscle function has also been reported in other chronic diseases *e.g.* chronic obstructive pulmonary disease [172] and cystic fibrosis [173], which might indicate a non-disease specific mechanism causing this phenomenon. Furthermore, positive effects of exercise training on muscle function have been reported in these latter patients groups [174-176]. Recently, positive effects of muscle training on muscle mass and strength was reported in a small group of patients palliated with Fontan procedure [113].

As expected a better muscle function, measured at heel-lift test and MIP/MEP, was observed in male patients compared to the females. This has previously been observed by others in patients with congenital heart disease [82] as well as in healthy [101]. These differences are generally explained by the differences in muscle mass distribution, where women have a greater proportion of their muscle mass distributed to the lower body [101, 177]. In order to compensate for this the females lifted a lower weight during the shoulder flexion test, which might explain the absence of gender difference regarding this test. In general men reach their peak strength between the ages of 20-30 while women reach it approximately at 20 years of age. Furthermore, skeletal- as well as respiratory muscle strength decreases with age [101, 149]. However, no association between age and muscle function was found in paper I which probably is explained by the homogeneity in age. In the general population, higher muscle strength in young age is associated

with a lower risk of developing cardiovascular disease later in life [178]. Additionally, impaired muscle strength is a predictor of mortality in patients with congestive heart failure [73, 76]. Whether the peak strength is lower or the decrease appears earlier in patients with congenital heart disease, is unknown. Furthermore the prognostic impact of impaired muscle function is not known and further research regarding muscle function in this group of patients is needed.

Height weight and BMI

In a recent study, on young patients palliated with Fontan procedure, shorter stature together with lean muscle mass deficit was observed [171]. In contrast, others have stated a normal muscle development in children and young adults palliated with Fontan procedure [179]. In the present thesis, it was shown that this difference is sustained into adulthood especially in men with complex lesions and also with some of the simple lesions. However, differences regarding body composition were less pronounced in women (paper III). These gender differences might suggest an influence of hormonal factors. Furthermore, reduced muscle function in combination with higher prevalence of underweight, lower prevalence of overweight/obesity and shorter stature indicates an altered body composition, especially in men with complex lesions. Cordina *et al.* observed a reduced muscle mass in adults palliated with Fontan procedure [79]. However, to what extent reduced muscle mass is present in patients with other congenital heart lesions is yet unknown.

The observation in the present thesis that adults with congenital heart disease generally followed the same pattern regarding BMI, as seen in the general population, raises concerns regarding increased risk of acquired cardiovascular disease. Overt obesity was only found in women with aortic valve disease. Moons *et al.* also reported of a higher prevalence of obesity in women but no further analysis of relation to diagnosis was made [129]. The combination of overweight/obesity, co-existing congenital heart disease together with previous cardiac surgery and potential need of intervention/re-intervention is of great concern. However, not only overweight/obesity is associated with increased all-cause mortality, underweight is also related with increased mortality [127, 180, 181]. In patients with congestive heart failure underweight is an important predictor of poor outcome [182] which in turn raises concerns about the cause and prognostic impact of presence of underweight in patients with complex lesions.

In the population of patients with complex lesions the great majority have previous surgical interventions. We found that this group of patients had

shorter stature compared to the general population. In addition, we found that patients with a previous intervention for VSD or ASD also were shorter compared to controls. This implies that previous intervention *per se*, which also is a marker of the severity of the lesion, might affect the final height at adult age.

Physical activity

In the general population, a low physical activity level in addition to a high energy intake is considered as two main factors causing development of overweight/obesity and thereby increased risk of acquired cardiovascular disease [121]. Furthermore, a low level of physical activity has been imposed to contribute to the lower exercise capacity found in patients with congenital heart disease [167]. However, in paper II we found that patients with congenital heart lesions, simple as well as complex, were equally active at a moderate-to-vigorous physical activity level as age and gender matched controls. Furthermore, our data on time spent at moderate-to-vigorous physical activity corresponds to data presented by others [93]. Previous reports on how recommendations on physical activity were reached in adults with congenital heart disease are contradictory. Müller *et al.* reported that a majority (72%) reached the recommendations on physical activity while, in contrast, Dua *et al.* reported that a minority were sufficiently active [94, 95, 183]. In a group of adolescents with complex congenital heart disease approximately 30% reached the recommendations [93]. We found that approximately 50% of patients as well as controls were insufficiently active to reach the recommendations. Recently it was reported that children with congenital heart disease were equally active as their healthy peers and that >50% of the children did not reach the current recommendations [92]. The finding that adults with congenital heart disease were equally active as the controls indicates that a low physical activity level might not have such great impact on the reduced exercise capacity found in adults with congenital heart disease. This probably leaves factors as abnormal cardiovascular anatomy and physiology to have a greater impact. Furthermore, in addition to the equalities found regarding physical activity level, the majority of adults with congenital heart disease followed the same pattern regarding BMI as seen in the general population (paper III). Previous studies have reported on the presence of traditional cardiovascular risk factors in adults with congenital heart disease [129, 130]. Insufficient physical activity level together with presence of congenital heart disease raises some concerns regarding the risks when acquired heart disease is added on pre-existing congenital heart disease. Over time, the prevalence of complications and the need of re-interventions due to the heart lesion increases [11] which in combination with the risk of acquired heart disease complicates the picture.

Primary prevention in order to prevent development of acquired cardiovascular disease may therefore be relevant in this population [129].

The higher count per day found in adults with simple lesions is however more difficult to explain. Nevertheless, accelerometer counts per day do not provide any information in the intensity of the activity. That is, someone may be more physically active at a lower intensity without reaching the recommendations of activity at moderate-to-vigorous level. Moreover, we found no differences regarding sedentary time. Sedentary time is considered as an important risk factor for development of cardiovascular disease and increased mortality [86, 87]. However, there is currently no cut-off value or consensus regarding what amount of time spent sedentary that is considered as more deleterious.

Health related quality of life (EQ-5D)

The majority of adults with aortic valve disease reported their health related QoL as best possible ($EQ\text{-}5D_{index}=1$) which reflects the results of previous studies regarding QoL in adults with different congenital heart lesions [161]. The association between higher physical activity level and a better QoL ($EQ\text{-}5D_{index}=1$) implies that QoL might be possible to affect by adopting a physically active life style. Many of the factors associated with impaired QoL ($EQ\text{-}5D<1$) as symptoms, lower educational level, active smoking and a higher systolic blood pressure may be possible to target with rehabilitation. Previous valve surgery, which might reflect the complexity of the heart lesion *per se,* is of course not possible to influence with rehabilitation. The variable "cardiovascular symptoms" was a composite variable comprised of different cardiac symptoms *e.g.* palpitations, dizziness, chest pain, tiredness, syncope, dyspnoea and oedema. This only provides information on presence of symptoms but not to what extent they were present or in which situations. Some symptoms *e.g.* dyspnea may be more prevalent during activity and thereby affect daily activities to a greater extent compared to others. On the other hand, palpitations due to ectopies might be more prevalent at rest and thus not limit physical activity. The association between a higher systolic blood pressure and impaired QoL is however more difficult to explain. A higher systolic blood pressure was not by definition hypertension but rather a slightly raised blood pressure and probably related to a higher age and thus the interpretation of this finding should be made with caution. The health related QoL is thus related to multiple factors of which most are modifiable through rehabilitation.

Exercise self-efficacy

The lower exercise self-efficacy found in adults with complex lesions in comparison to controls is consistent with previous reports, although they lacked control group [95, 110]. In adolescents with congenital heart disease a correlation between physical activity level and exercise self-efficacy has been observed [184]. These results might reflect an uncertainty regarding suitable activities which in turn might be an effect of previous overprotection by parents or relatives [167] and inappropriate information regarding suitable activities given by health care providers [168]. Evaluation of exercise self-efficacy could serve as an important complement in assessment prior to the design of an individual exercise training program. It has previously been reported that many patients with congenital heart disease overestimate their exercise capacity [47]. However, discrepancies regarding suitable training mode, intensity, duration and frequency can go in both directions. Although speculative, in a patient with severely reduced exercise capacity and a relatively high confidence in physical exercise, this could indicate a person prone to overloading. Furthermore, the opposite scenario could indicate a person prone to underestimation of their capacity.

Physiotherapy intervention

We found that individually adjusted interval training on ergometer cycle increased the peak VO_2 in the intervention group but not in comparison to controls, which probably reflects the relatively small sample size. However, peak work load and endurance capacity increased in comparison to controls. The incremental CPET is considered as the "gold standard" in evaluation of exercise capacity [119]. In rehabilitation of patients with COPD, the constant work rate test has emerged as a useful complement to the incremental CPET [155, 156]. Furthermore, it has been observed to be a more responsive test in evaluation of rehabilitation interventions [157]. Although peak exercise capacity is an established measure and important predictor of outcome, a test reflecting endurance capacity might serve as a complement in rehabilitation of adults with congenital heart disease. A measure of endurance might even reflect the capability of coping with daily activities to a better extent then a peak exercise test. We observed that a relatively small change in peak exercise capacity resulted in a substantially larger proportional improvement in endurance.

Complexity of lesion and NYHA class

When analysing muscle function (paper I), complexity of lesion emerged as a predictor of impaired muscle function. However complexity of lesion is

related to a number of factors which are potential confounders *e.g.* the number of previous surgical interventions [185], impaired pulmonary function [70], ongoing medications, inappropriate advice regarding physical activity and overprotection [168, 186]. Therefore, it is difficult to evaluate single variables of importance. I addition to reduced muscle function, we found deviations in height, weight and BMI, especially in men with complex lesions (paper III). This might indicate physiological effects of the complex heart lesion on body composition. The reason for the less pronounced differences found in women with corresponding lesions suggests hormonal effects as well. Others have reported of an association between impaired muscle function and NYHA class [82].

Complexity of lesion was not associated with physical activity level (paper II), which means that also those with complex lesions were equally active at moderate-to-vigorous level as controls. However, with NYHA class I as reference, being in NYHA class III was associated with more time spent in moderate-to-vigorous physical activity level. Moreover, NYHA class II was associated with less time spent at this level. This is probably explained by the more pronounced impairment of exercise capacity found among patients in NYHA class III that results in daily activities being more strenuous [4]. This was partly in conflict to previous observations by others where those in NYHA class III were found to be less physically active [95]. This can however be related to the different measurements applied. In patients with simple lesions, the absence of regular exercise training in addition to impaired NYHA class, that might reflect more physically limited individuals, was found to be associated with a higher BMI (paper III).

NYHA class was originally a subjective measure of limitation in daily activities due to dyspnoea in patients with heart failure. However in clinical practice it is also used in estimation of limitation due to angina pectoris. The relation between complexity of congenital heart disease and NYHA functional class is nevertheless complex *i.e.* a patient with a complex congenital heart disease can be in NYHA class I. This is also reflected in the large variation of exercise capacity within each diagnosis group [4]. NYHA class might underestimate the true degree of exercise limitation [3], nevertheless, NYHA class rather than the complexity of the diagnosis might be more important to consider in the clinical setting.

Sex differences

In concordance to others we found that men were more physically active at moderate-to-vigorous level [95, 129]. However, no sex difference regarding physical activity level has been observed by others [94]. Sex differences were,

as expected, also found regarding muscle function which has previously been observed by others in patients with congenital heart disease [82] as well as in healthy [101]. Interestingly we found more pronounced differences regarding height, prevalence of underweight and overweight/obesity in men with congenital heart disease indicating an altered body composition. Although speculative, it might be that the heart lesion affects hormonal regulation, responsible for muscle development. However, further analysis of "true" body composition and muscle composition is needed to investigate underlying mechanisms.

Methodological considerations

The muscle function tests, shoulder flexion and heel-lift, are clinically suitable tests not reliant on advanced equipment. These tests were originally validated in patients with congestive heart failure [148] and are also used in the current clinical routine. Furthermore, these tests have previously been used in evaluation of muscle function in adults with congenital heart disease [82]. In research evaluation of isokinetic muscle strength is commonly used. However that method requires access to rather complex, expensive and usually stationary equipment [187]. All muscle function tests were instructed and supervised by the same person thus reducing differences in assessment.

Regarding objective estimation of physical activity using wearable monitors it is difficult to compare results of studies that used different equipment. This due to different inherent estimation equations used to convert the collected "raw" accelerometer data into "counts". In addition, the cut-off to define moderate-to-vigorous activity differs between accelerometers [89, 91]. Furthermore, the epoch length used in different studies varies. Finally, adjustment for wear time in the analyses, as made in the present thesis, has recently been reported to be important in order to present as accurate results as possible [188]. Corresponding adjustments were not reported in previous reports on physical activity in adults with congenital heart disease [43, 95, 183].

Body mass index (kg/m^2) is a widely used measure of prevalence of underweight, overweight and obesity. In combination with waist circumference or hip waist ratio it provides a more accurate picture of the prevalence of abdominal obesity [120, 121]. However, it does not provide a measure of the true body composition (muscle mass and fat mass). To assess this, dual-energy x-ray absorptiometry (DEXA) could be used [189]. However the access to this method is limited, which makes it more difficult to use in larger populations. Furthermore, the usage of BMI is vitiated with a risk of misclassifying patients with a high BMI due to a large muscle mass

[131, 132]. However, in a relatively large population this would be diluted due to the expected low number of persons active at on a level that results in high BMI due to large muscle mass [133]. Furthermore, data regarding height and weight in patients that was extracted from SWEDCON were originally obtained as a routine during clinical visits. The corresponding data in the control population was obtained via telephone interviews that may taint the results with bias [190, 191]. However, the fact that the majority of adults with simple lesions did not differ from the controls might serve as an internal validation in favour of the controls.

The EQ-5D questionnaire is a rather rough instrument to use in evaluation of QoL on an individual basis. In a large registry, however, it is an easy instrument to use to evaluate QoL on group level. Furthermore, there is no existing consensus on how to define QoL. Previously it has been argued that reasons for impaired QoL are quite individual and thereby better reached through deeper questions regarding this topic. Moreover, sense of coherence has emerged as an important factor to take into consideration and data has indicated that QoL may be possible to affect by targeting the sense of coherence; the better sense of coherence the higher QoL [135].

The exercise self-efficacy scale was originally developed for persons with neurological diseases [163, 164], but has previously been used in patients with COPD as well [165]. No apparent problem using this scale in adults with congenital heart disease was detected. Moreover, exercise self-efficacy has been evaluated in patients with congenital heart disease previously with similar results as in the present thesis, although using other questionnaires [95, 110].

Clinical implications and further research

In a patient population with large diversity regarding diagnoses, exercise capacity and symptom presence [3, 4, 6, 11], individualised exercise prescription is highly important [107]. Moreover, exercise capacity and symptom presence may change over time [11, 44], implying that individualised exercise prescription with regular follow-up is essential. Current clinical practice includes regular evaluation of exercise capacity. Corresponding evaluation of muscle function by physiotherapists would also be reasonable as this could provide a more complete overview of the patient´s current state and facilitate monitoring of disease development over time. Such practice might also increase the probability of detecting disease deterioration. Furthermore, baseline evaluation of muscle function, physical activity level and exercise self-efficacy should be performed to aid in prescribing exercise training.

The substantially larger effect on endurance capacity compared to peak exercise capacity raises the interest in using constant work rate CPET when evaluating the effects of aerobic exercise training in this population. The results suggest that this might be a more responsive test which is in agreement with previous findings in patients with COPD [157]. However, this method requires further evaluation.

The majority of studies investigating exercise training in adults with congenital heart disease have evaluated aerobic training (Table 8-10) [80, 108-117]. However, the impaired muscle function in addition to indications of altered body composition in this population highlights the need for further research regarding “true body” composition, muscle composition, muscle metabolism and the effects of muscle training [79, 82, 113].

Conclusions

- Adults with complex congenital heart disease had impaired skeletal and respiratory muscle function in comparison to patient with simple lesions and age- and gender matched controls.

- Adults with complex congenital heart disease had lower exercise self-efficacy in comparison to and age- and gender matched controls.

- Adults with simple congenital heart disease had higher accelerometer counts per day compared to those with complex lesions and controls.

- Adults with congenital heart disease were equally active at a moderate-to-vigorous physical activity level in comparison to age- and gender matched controls.

- Approximately 50% of both patients and controls were insufficiently active to reach the current recommendations on physical activity.

- Men with congenital heart disease had a higher prevalence of underweight and lower prevalence of overweight/obesity compared to population data.

- Men with complex congenital heart disease and those VSD were shorter and in addition, men with AS/AR, VSD, PA/DORV and those palliated with Fontan/TCPC had a lower BMI. Only limited differences were found in women with corresponding lesions.

- The majority of adults with congenital heart disease follow the same distribution of overweight/obesity as seen in the general population. The association between overweight/obesity and increased risk of acquired cardiovascular disease in combination with a present congenital heart disease and thereby a potential need of surgical re-intervention is of great concern.

- A higher physical activity level *i.e.* exercise training ≥3hrs/w was associated with a higher QoL (EQ-5D_{index}=1). This implies that QoL might be influenced by adopting a physically active lifestyle.

- Previous valve surgery, together with factors possible to target with rehabilitation *i.e.* presence of cardiovascular symptoms, active smoking, lower educational level and a higher blood pressure were associated with impaired QoL ($EQ\text{-}5D_{index<1}$).

- Home-based interval training increased exercise capacity and endurance in adults with complex congenital heart disease.

Appendix

Träningsprogram vecka 1 och 2		
Uppvärmning Cykla obelastat eller med mycket lätt belastning	8 min	Borgs RPE 9-11
Belastningstopp 1 Vrid upp belastningen så att pulsen ligger mellan	___ min	Borgs RPE 14-16
Aktiv återhämtning Obelastat eller mycket lätt belastning	3 min	
Belastningstopp 2 Vrid upp belastningen så att pulsen ligger mellan	___ min	Borgs RPE 14-16
Aktiv återhämtning Obelastat eller mycket lätt belastning	3 min	
Belastningstopp 3 Vrid upp belastningen så att pulsen ligger mellan	___ min	Borgs RPE 14-16
Nedvarvning Cykla obelastat eller med mycket lätt belastning	5 min	
Total träningstid:		

Träningsprogram vecka 3-12		
Uppvärmning Cykla obelastat eller med mycket lätt belastning	8 min	Borgs RPE 9-11
Belastningstopp 1 Vrid upp belastningen så att pulsen ligger mellan	___ min	Borgs RPE 14-16
Aktiv återhämtning Obelastat eller mycket lätt belastning	3 min	
Belastningstopp 2 Vrid upp belastningen så att pulsen ligger mellan	___ min	Borgs RPE 14-16
Aktiv återhämtning Obelastat eller mycket lätt belastning	3 min	
Belastningstopp 3 Vrid upp belastningen så att pulsen ligger mellan	___ min	Borgs RPE 14-16
Aktiv återhämtning Obelastat eller mycket lätt belastning	3 min	
Belastningstopp 4 Vrid upp belastningen så att pulsen ligger mellan	___ min	Borg RPE 14-16
Nedvarvning Cykla obelastat eller med mycket lätt belastning	5 min	
Total träningstid:		

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