TECHNISCHE UNIVERSITÄT MÜNCHEN

Klinik für Kinderkardiologie und angeborene Herzfehler
Deutsches Herzzentrum München (DHM)

Lehrstuhl und Poliklinik für Präventive und Rehabilitative Sportmedizin

Daily activity, exercise physiology and quality of life in adolescents and adults with congenital heart disease

Jan Müller

Vollständiger Abdruck der von der Fakultät für Sport- und Gesundheitswissenschaft der Technischen Universität München zur Erlangung des akademischen Grades eines

Doktors der Naturwissenschaften (Dr. rer. nat.)

genehmigten Dissertation.

Vorsitzende: Univ.-Prof. Dr. Renate Oberhoffer

Prüfer der Dissertation:

1. Priv.-Doz. Dr. Alfred Hager
2. Univ.-Prof. Dr. Martin Halle
3. apl. Prof. Dr. Josef Högel, Universität Ulm

Die Dissertation wurde am 8.10.2010 bei der Technischen Universität München eingereicht und durch die Fakultät für Sport- und Gesundheitswissenschaft am 10.05.2012 angenommen.

I. Abbreviation

ADS	Allgemeine Depressionsskala
AS	Aortic valve Stenosis
ASD	Atrial Septal Defect
AVSD	AtrioVentricular Septal Defect
CHD	Congenital Heart Disease
CPET	Cardio Pulmonary Exercise Test
CoA	Coarctation of the Aorta
ES	Eisenmenger Syndrome
HLH	Hypoplastic Left Heart
HRH	Hypoplastic Right Heart
MET	Metabolic Equivalent
PAH	Pulmonary Arterial Hypertension
PFO	Patent Foramen Ovale
PDA	Persistent Ductus Arteriosus
PS	Pulmonary valve Stenosis
TAC	Truncus Arteriosus Communis
TCPC	Total CavoPulmonary Connection
TGA	Transposition of the Great Arteries
ToF	Tetralogy of Fallot
TV	Tricuspid Valve
VSD	Ventricular Septal Defect

II. Table of Figures

III. List of Tables

1. Introduction

Survival in congenital heart disease (CHD) has increased substantially due to improved surgical techniques, advanced diagnostic methods, and more sophisticated medical management.[88] Recently, the number of adolescents and adults with CHD is rapidly increasing and in the near future, will exceed that of the pediatric age group.[71]

However, a substantial proportion of this group still expect further medical and surgical intervention. In addition, this increasing group of patients has to face particular challenges and concerns beyond cardiology like psychosocial issues, emotional difficulties, educational delays, sexuality and pregnancy. Patients have to cope with these issues in their daily life.[38, 75, 101, 115-117] It is for this reason that the success of medical, surgical or interventional treatment is no longer measured by survival, need for redo-procedures, or cardiac function variables, but rather by global physical capacity, or even quality of life.[38, 88, 117]

The increased life expectancy now raises another important issue: The need for regular physical activity to prevent metabolic diseases like overweight, hypertension and diabetes in the future.

Traditionally, these patients were withheld from physical exercise because of the fear of heart failure or sudden cardiac death. Physicians often believe they are “on the safe side” when they restrict physical activity coupled with parental overprotection in childhood.[77, 106] Those patterns of inactivity may lead to reduced exercise capacity,[30, 80] delayed motor and strength development[5, 68] and overweight.[103] All these issues contribute to impairments in social skills and psychosocial problems[102] and curtail quality of life and probably life expectancy in this patient cohort.[51]

Nowadays, since several smaller studies have proven that exercise in the majority of patients with CHD is safe,[33, 40, 108] contemporary consensus documents state: “Regular exercise at recommended levels can be performed and should be encouraged in all patients with congenital heart disease”.[56] However, they forgot to mention that it might be difficult to promote physical activity to those who were forbidden to do so for such a long time.

2. Objective

The foundation of this study is based on two major objectives:

1. Gain insight on the daily activity patterns of adolescents and adults with congenital heart disease, as to whether they participate in vigorous or leisurely activities and to analyze how their activities are associated with exercise performance and quality of life.

2. Depict psychological issues like depression and anxiety and their interaction with exercise capacity and quality of life in the vast cohort of patients with congenital heart diseases.

3. Medical Background

As shown in Table 1, the human heart bears many different kinds of malformations that can appear in isolated or in combined forms. In some cases, very complex forms exist including several different single diagnoses.
Normally CHD are differentiated in cyanotic and acyanotic. For a better understanding, this dissertation focused on the ten major subgroups as they are presented later on in the research part. This will lead to a better understanding of the common heart failures in the future.

Heart malformation	No. of patients	Prevalence per 1000 live births	% of all heart malformations
Ventricular septal defect	2092	2.56	41.59
Atrial septal defect	436	0.53	8.67
Aortic stenosis	391	0.48	7.77
Pulmonary stenosis	292	0.36	5.81
Transposition of the great arteries	271	0.33	5.39
Coarctation of the aorta	266	0.33	5.29
Persistent ductus arteriosus	255	0.31	5.07
Atrioventricular septal defect	201	0.25	4.00
Hypoplastic left heart	172	0.21	3.42
Tetralogy of Fallot	169	0.21	3.36
Double-outlet right ventricle	69	0.08	1.37
Single ventricle	67	0.08	1.33
Persistent truncus arteriosus	55	0.07	1.09
Pulmonary atresia with ventricular septal defect	55	0.07	1.09
Pulmonary atresia with intact ventricular septum	53	0.06	1.05
Total anomalous pulmonary venous drainage	40	0.05	0.80
Tricuspid atresia	39	0.05	0.78
Ebstein's anomaly of the tricuspid valve	22	0.03	0.04
Interrupted aortic arch	19	0.02	0.38
Anomalous origin of the left coronary artery	11	0.01	0.22
Others	27	0.03	0.53
Total	5030	6.16	100.00

Table 1: Prevalence of Congenital Heart Diseases.[97]

3.1. Isolated Shunts

Isolated shunts are the most common heart defects that can appear at the level of the veins, atria, ventricle and arteries. Generally they were differentiated in pre-tricuspid or post-tricuspid, or in the flow or pressure shunts. Regardless of the anatomical location, the physiologic consequence of a shunt is the result of the shunting of blood from one heart-side to the other. The direction and magnitude of shunting are determined by the location, size of the defect and the relative compliance of the ventricles (Figure 1).

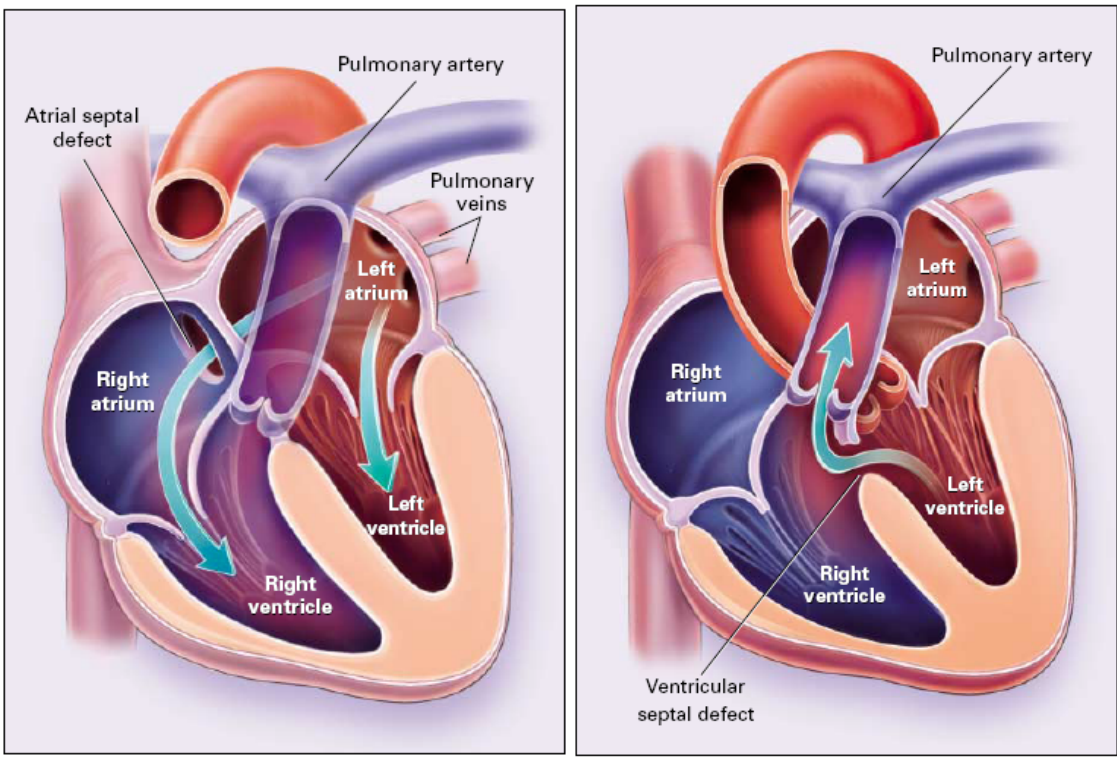

Figure 1: Atrial Septal Defect (left) and Ventricular Septal Defect (right) with a Resultant Left-to-Right Shunting.

A flow or pre-tricuspid shunt is indicated by an increased blood flow on the level of the veins or atria. The anatomic origin of pre-tricuspid shunts is located before the blood passes the tricuspid valve. More often than not, this is an Atrial Septal Defect (ASD), a Persistent Foramen Ovale (PFO) or a partial AtrioVentricular Septal Defect (pAVSD). Partial or total anomalous pulmonary venous connections are also forms of pre-tricuspid shunt on the level of the veins.

Due to the pressure gradient, the direction of the shunt is from left-to-right. This causes an additional volume load on the right heart side and an increase in lung perfusion, which leads to right ventricular dilatation. If left untreated, this leads to arrhythmia and right heart failure over the years.[10]

On the contrary, a pressure or post-tricuspid shunt's origin is on the level of the ventricles or arteries. Complete AtrioVentricular Septal Defect (cAVSD), Ventricular Septal Defect (VSD) and Patent Ductus Arteriosus (PDA) are the most common. The aortopulmonary window, a small communication between the ascending aorta and the pulmonary artery; and the Truncus Arteriosus Communis (TAC) where the embryological structure known as the truncus

arteriosus never divides into the pulmonary artery and aorta, are very rare forms of post-tricuspid shunts.

In post-tricuspid shunts, there is also left-to-right shunting with increased pulmonary blood flow. The major difference however, is that the shunting blood is pumped to the lungs with high pressure from the left ventricle. If untreated, majority of patients with unrestrictive shunts at post-tricuspid level will develop remodelling of the vascular bed and early irreversible Pulmonary Arterial Hypertension (PAH), which leads to irreversible shunt reversal called the Eisenmenger Syndrome (Chapter 3.9.). Whereas in patients with pre-tricuspid shunting, the development of PAH is delayed over decades. Fortunately, many small ASDs or VSDs close spontaneously in early childhood and some of the persistent defects in the septal are of small size and not associated with hemodynamic burden.

Major shunts with hemodynamic relevance should be closed surgically or occluded with a percutaneously placed closure device. When patients show symptoms, they typically report fatigue or dyspnea upon exertion. Alternatively, the development of sequels like supraventricular arrhythmias, right heart failure, paradoxical embolism or syncope may prompt the patient to seek medical attention. In those cases, the shunt should be closed surgically or occluded with a percutaneously placed closure device to prevent right ventricular dysfunction and pulmonary vascular disease in the future.[63]

After shunt closure, majority are assumed to be cured without limitations in daily life and exercise. Nevertheless, arrhythmia, due to operative scars and heart failure, are rare sequels in patients with isolated shunts.

3.2. Aortic Valve Stenosis

Aortic valve Stenosis (AS) is a narrowing of the aortic valve orifice or of the aorta above (supra) or below (sub) the valve. Its severity is determined by the obstruction of the blood flow to the Aorta. Due to this obstruction, left ventricular pressure increases to maintain the blood pressure in the Aorta. Severity of stenosis is typically determined by the pressure gradient across the valve measured by ultrasound.

To compensate for the increasing resistance at the aortic valve, the muscles of the left ventricle thickens to maintain pump function and cardiac output. This may not cause any problem at rest, but an increase in output with exercise may be limited. The classic symptoms of AS are related to exercise such as angina pectoris, and syncope or dyspnea that is caused by an increased demand on the heart muscle for oxygen and insufficient coronary filing in the shortened diastole.. Therefore, asymptomatic patients should be screened regularly by exercise testing if they show symptoms during exercise. Syncope or near-syncope can also appear because of the Bezold-Jarisch reflex resulting to bradycardia and vasodilatation. In addition, shortness of breath due to an increased pressure required to fill the left ventricle may appear.

Patients often are asymptomatic for a long time and their exercise performance[30] and quality of life[78, 80] is best for patients with CHD. Once symptoms appear however, survival is dramatically limited.[10, 17] Possible Intervention could be percutaneous balloon valvuloplasty if the insufficiency component of the valve is small. Otherwise, surgical reconstruction or valve replacement is required to preserve event free survival.

Moreover, special relevance should be given to bicuspid aortic valves found in 2-3 percent of the population. Those patients may be asymptomatic for a long time because the deformed valve is not stenotic at birth, but subjected to abnormal hemodynamic stress. This may lead to the thickening and calcification of the leaflets which results to immobility later in life.[10]

3.3. Coarctation of the Aorta

Aortic coarctation (CoA) is a congenital condition whereby the aorta is narrowed in the area where the ligamentum arteriosum inserts. This coarctation causes an obstruction of the blood flow to the descending thoracic aorta (Figure 2).

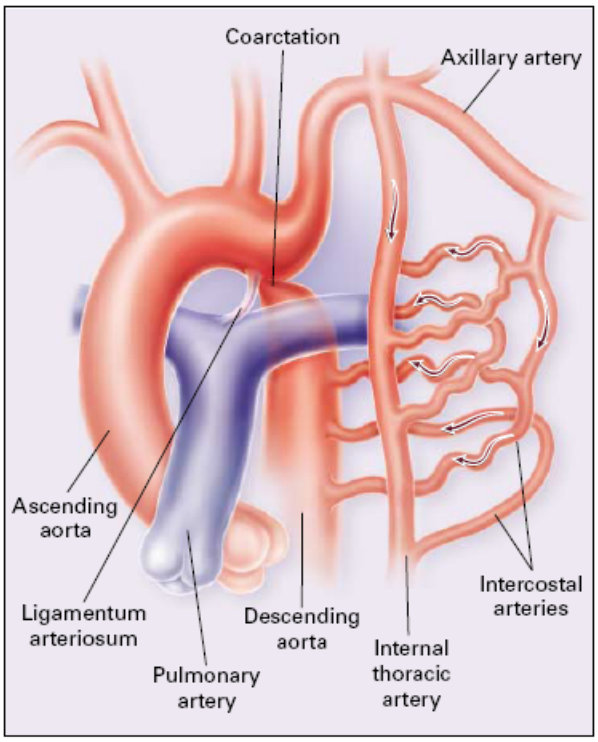

Figure 2: Coarctation of the Aorta. Descending aorta and its branches are perfused by collateral channels from the axillary and internal thoracic arteries through the intercostal arteries.

It is only in severe forms where symptoms like irritability, pale skin or sweating or seek physical attention thru a heart murmur during an examination in early childhood may be experienced. There are mild forms that may be asymptomatic for a long time and the diagnosis is made during routine physical examination, when systemic arterial hypertension is observed in the arms, with diminished or there is absence in femoral arterial pulses.[10] As for patients with aortic stenosis, left heart hypertrophy occurs to maintain cardiac output. In contrast to patients with aortic stenosis, this hemodynamic burden could be measured in brachial blood pressure. Hence, the degree of blood pressure decrease from the right arm to the legs could separate those with mild forms from the severe ones and serves as a sign for the necessity of intervention. Moreover, due to left ventricular adaptation there is no impairment in exercise performance in majority of patients with CoA.[30, 78]

In the past, repair was performed mainly by surgery where the narrowed segment with the adjacent ductus arteriosus is restricted and the two ends of the aorta are sewn together.[24] Recently, ballondilatation or stent implantation is also performed. Postoperative complications include residual or recurrent

hypertension and coarctation.[10] In cases of re-coarctation, the usual method used to stretch the area open is catheter intervention. This is done using a balloon and/or placing a stent to keep the section open.

Finally, CoA should be considered as a complex cardiovascular syndrome rather than an isolated narrowing of the aortic isthmus. Bicuspid aortic valve, VSD and cerebral aneurysm are found in many patients with CoA.[10] Moreover, wall abnormalities were found not only in the ascending and descending aorta. This results to an increased stiffness of the aorta and carotid arteries and an augmented pulse wave velocity. All of these pathologic conditions, including re-stenosis, contribute to an increased cardiovascular morbidity and mortality such as coronary artery disease, stroke and heart failure.[54]

3.4. Pulmonary Valve Stenosis

Same as with patients with aortic stenosis, an obstruction exists due to a narrowing, mainly, directly at the orifice of the pulmonic valve which curtails the lung perfusion and increases right ventricular pressure; leading to right ventricular hypertrophy.[10]

When stenosis becomes severe, symptoms like dyspnea upon exertion, fatigability or right heart failure may occur. In patients where a foramen ovale is apparent, shunting of blood from the right to the left atrium may appear, causing cyanosis that might increase under exercise. A surgical intervention should be considered, removing the stenosis and, if present, closing the shunt.

The first palliative surgically procedures to increase lung perfusion were done by Alfred Blalock and Helene Taussig.[8] Later on Brock procedure[12] was used to open the valve with a finger punch. Since the 80's, relief of valvular stenosis is normally accomplished easily and safely with percutaneous balloon valvuloplasty[59] with excellent short and long-term outcome with regards to exercise[78], quality of life[80] and survival[18] at any age of the intervention. A valve replacement is only required if the leaflets are dysplastic, calcified or if severe regurgitation is present.[10]

3.5. Ebstein Anomaly

Ebstein anomaly is a rare isolated congenital malformation occurring in <1% of all cases of CHD. It is characterized by a downward displacement of the tricuspid valve into the right ventricle reducing the effectivity of the right ventricular volume, an enlarged redundant anterior leaflet and an adherence of the septal and/or posterior leaflets to the underlying myocardium. Tricuspid regurgitation and right heart failure are the leading clinical findings. Its severity is the bases of the different constellations of tricuspid malformation.[1, 98] An interatrial communication is present in 80% to 94% of patients with Ebstein's anomaly.[1, 11] Most often this is a Patent Foramen Ovale that opens with increased right atrial pressure. During exercise, these patients suffer from cyanosis, dyspnea and exercise intolerance caused by right heart failure and interatrial right-to-left shunting (Figure 3).[69]

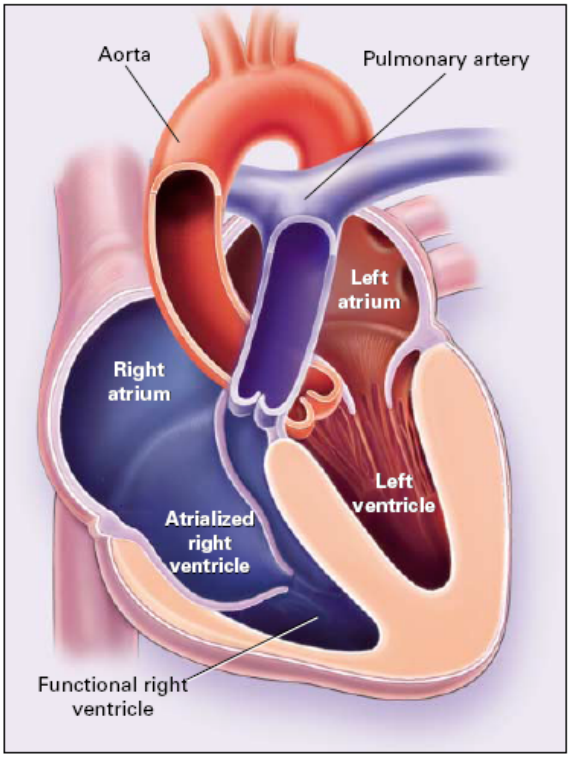

Figure 3: Ebstein's Anomaly. Showing an atrialized right ventricle

In Ebstein's anomaly there are patients with mild forms having normal life-spans and in good conditions without surgery. Many other patients however, require surgery but the appropriate timing for intervention often remains unclear.[3, 14] Nevertheless when functional status deteriorates through an increase in right heart size and reduction in systolic function surgery is urgently indicated to

preserve right ventricular function.[1, 3] A decrease in exercise performance and proceeding cyanosis under exercise are also indications for intervention.[81]

3.6. Tetralogy of Fallot

Étienne Fallot was the first in describing one of the most common cyanotic CHD in 1888. It is characterized by a large ventricular septal defect, an aorta that overrides the left and right ventricles, and an obstruction of the right ventricular outflow tract which results in right ventricular hypertrophy (Figure 4).[36] A more contemporary defines “malalignment VSD” as the primary defect resulting in the three other findings.

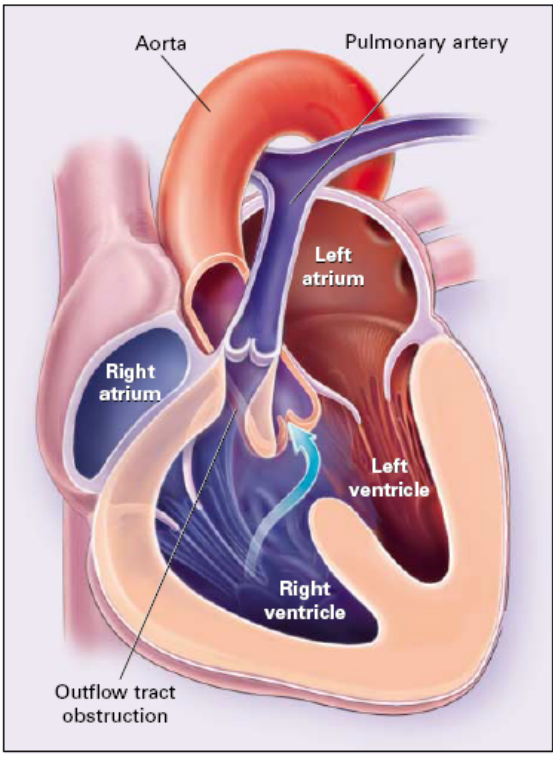

Figure 4: Tetralogy of Fallot. With substantial obstruction of the right ventricular outflow tract, blood is shunted through the ventricular septal defect from right to left.

Brought about by the large VSD, the right and left ventricular pressures are similar. Right-to-left shunting of venous blood occurs because of increased resistance in the right ventricular outflow tract, the severity of which determines the magnitude of shunting.[11]

Without surgical intervention, most patients die in childhood. The rate of survival is 66 percent at 1 year of age, 40 percent at 3 years, 11 percent at 20 years, 6 percent at 30 years, and 3 percent at 40 years.[4] Hence, complete surgical

correction requiring the closure of the VSD and relief of right ventricular outflow tract obstruction is performed in infancy.

In this dissertation, patients with Double Outlet Right Ventricle (Aorta and pulmonary artery arise both from the right ventricle) or Pulmonary Atresia with a Ventricular Septal Defect (PA-VSD) are also referred to the Tetralogy of Fallot section. The reason for this grouping is that after the corrective surgery that is normally done in infancy, the hemodynamic situation is nearly similar. Generally, the VSD was closed with a patch and lung perfusion was relieved either with the implantation of an allograft or with a patch in the right outflow tract.

However, stenosis and insufficiency of the conduit usually occur in the sequel and force re-operations to avoid right ventricular dysfunction, incidence of arrhythmias thru an enlargement of the right ventricle, or even sudden death.[11, 42, 43, 61] Re-intervention is basically done by surgery where the outflow tract is renewed with a conduit. Nevertheless, long term survival[82] and quality of life[80] is good in those patients, despite minor limitations in exercise capacity.[78]

Fortunately, many patients are already eligible for a percutaneous replacement of the pulmonary valve in the catheter lab.[9]

3.7. Transposition of the Great Arteries

In Transposition of the Great Arteries (TGA or d-TGA) pathophysiologically the aorta arises in an anterior position from the right ventricle and the pulmonary artery arises from the left. In order to survive, there must be a communication between the two circuits permitted by a PFO, PDA, ASD or VSD (Figure 5).

Without intervention, prognosis is poor and the mortality rate is up to 90 percent by six months of age which makes early surgical intervention essential.[11] This evolution and progress in surgical intervention of TGA is an important and fascinating story of man's ingenuity in dealing with CHD.

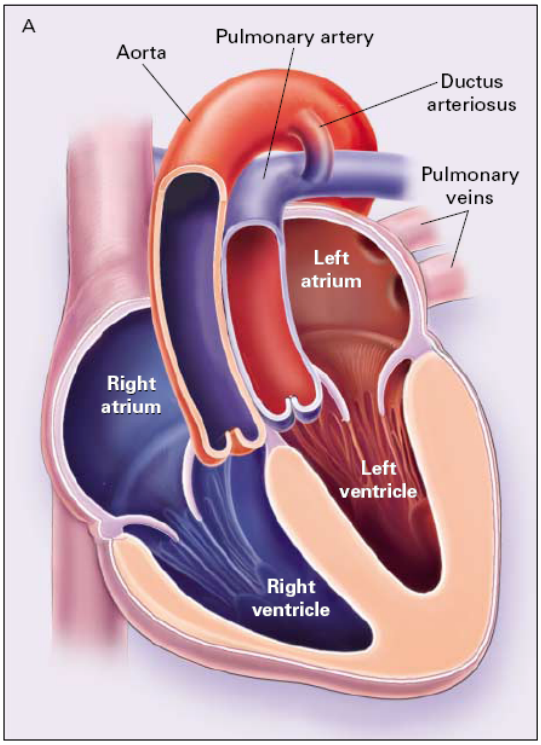

Figure 5: Transposition of the Great Arteries (TGA) also named d-TGA

First, palliative procedures described by Blalock and Hanlon[7] or Rashkind[91] improved cardiac shunting and eased cyanosis. However, the initial approach were two different types of “atrial switch” procedures developed nearly simultaneous in the early 60’s by Senning[100] and Mustard[83] (Figure 6).

The restored physiologic circulation with in intra-atrial baffle eliminated cyanosis and extended survival. However, it was just another palliative procedure, since the right ventricle continued to function as a “systemic left ventricle”. Since Jatene[57] resurrected and superseded the concept, “arterial switch”, also known as anatomic procedure, is the method of choice since the early 80’s for almost all of the patients born with TGA. Therefore, pulmonary artery and ascending aorta are transacted above the valves and switched such as the coronary arteries, which result in a normal circulation (Figure 7).

For research purposes, it is now important to differentiate patients having a systemic right ventricle after an atrial switch (Senning and Mustard) from patients with systemic left ventricle after an arterial switch (anatomic repair) because sequels are completely different.

3.7.1. TGA after Atrial Switch (Senning or Mustard)

The Senning[100] and Mustard[83] operations revolutionized the care of patients with TGA, but along with increasing age, the right ventricle that has to function as a systemic ventricle, gets dilated and impaired in its function.

Baffle obstruction, sinus-node dysfunction and atrial arrhythmias, as well as tricuspid regurgitation and right ventricular dysfunction leads to impairment in exercise capacity, [45, 78] increased risk of heart failure and sudden death.[11, 32, 45]

Surgical repair of the baffle stenosis or replacement of the tricuspid valve and pacemaker implantation are common causes for re-operation in addition to drugs for heart failure. Heart transplant is the last option for specially selected patients.

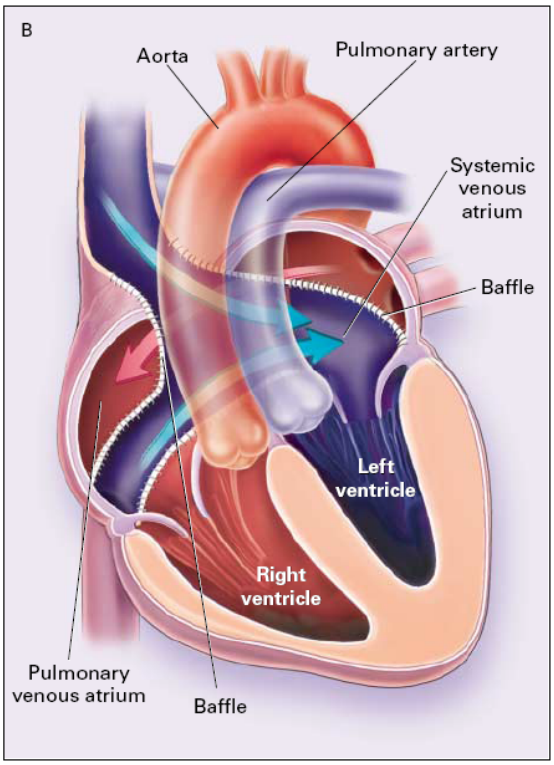

Figure 6: TGA after an atrial switch procedure with in intra-atrial baffle (Mustard procedure)

Even though this procedure has become obsolete, there remains a large cohort of adults who underwent atrial redirection in childhood.

3.7.2. TGA after Arterial Switch (anatomic repair)

Arterial-switch operation replaced the Senning or Mustard operation because of an excellent long-term outcome. The main result is the normal ventricular

circulation that provokes no dilation in the right heart size. Thus, tricuspid regurgitation and right heart failure are, same as arrhythmias, less frequent after the anatomic procedure. This results in a better exercise ability in patients after the atrial switch.[30, 78, 80]

This sophisticated procedure however, bears complications later in life. Pulmonary stenosis and stenosis in the pulmonary arteries are the major problems caused by a forward displacement of the pulmonary truncus anterior to the aorta.

Moreover, further long term sequels could mean that re-implanting the coronary arteries may lead to myocardial ischemia and myocardial infarction. In addition, switching the vessels near the valves may lead to insufficiency or stenosis.

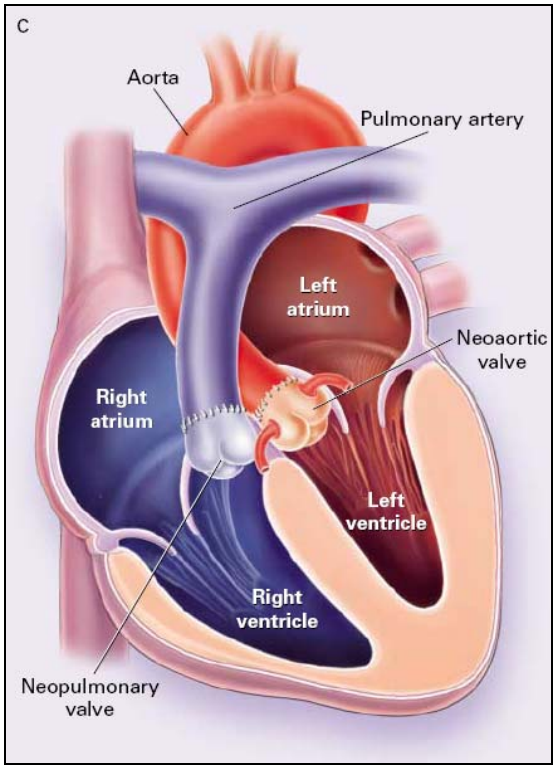

Figure 7: TGA after an aterial switch (anatomic repair)

3.8. Fontan Circulation

Generally, “Fontan Circulation” is a collective term for those kinds of complex CHD not suitable for a bi-ventricular repair. Often it is spoken from a “single ventricle”. However, this is incorrect because in almost all patients a dominant and an underdeveloped hypoplastic ventricle exist. An absent tricuspid valve causes an underdevelopment of the right ventricle leading to a hypoplastic right

ventricle. Analogue mitral atresia causes hypoplastic left heart syndrome (HLH). Nowadays, these are the most common diagnosis a Fontan procedure is indicated. Unfortunately, sometimes it is much more complex (Figure 8).

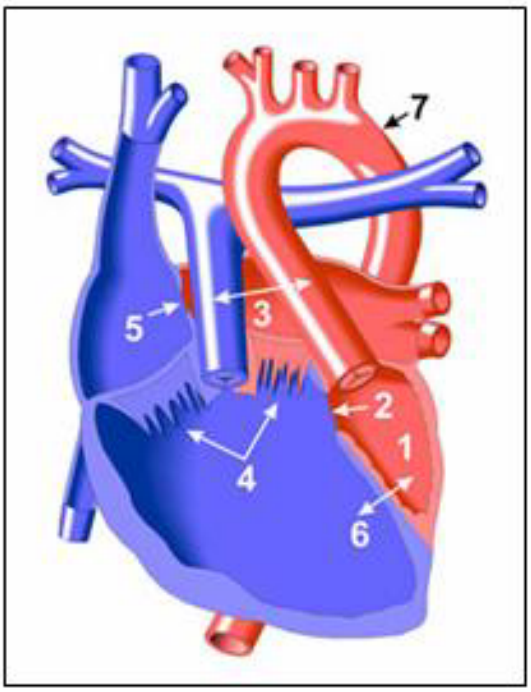

Figure 8: Double Inlet Left Ventricle with transposition of the great arteries (DILV with l-TGA)

Palliative surgical treatment was first described by Fontan and Baudet[37] in 1971. It involves diverting the venous blood from the right atrium to the pulmonary arteries without passing through the morphologic subpulmonary ventricle. This eliminated cyanosis and prolonged survival. Over the years, several modification developed from Kreutzer[65], Björk[6] and Lins.[67] Arrhythmia as a severe long-term sequel resulting from a dilated atrium and operative scars could not however be reduced. Thus the major advances in this procedure were done by de Leval[27] and Marcelletti[70] in the late 80's. The right heart side is now completely bypassed by an intra-arterial baffle or an extracardiac conduit and the blood flow to the lungs became less turbulent. The generated method was named total cavopulmonary connection (TCPC) in either lateral[27] or more common, extracardiac[70] accomplishment (Figure 9). Nevertheless, it still remains a palliative and not a corrective surgical treatment of the malformation.

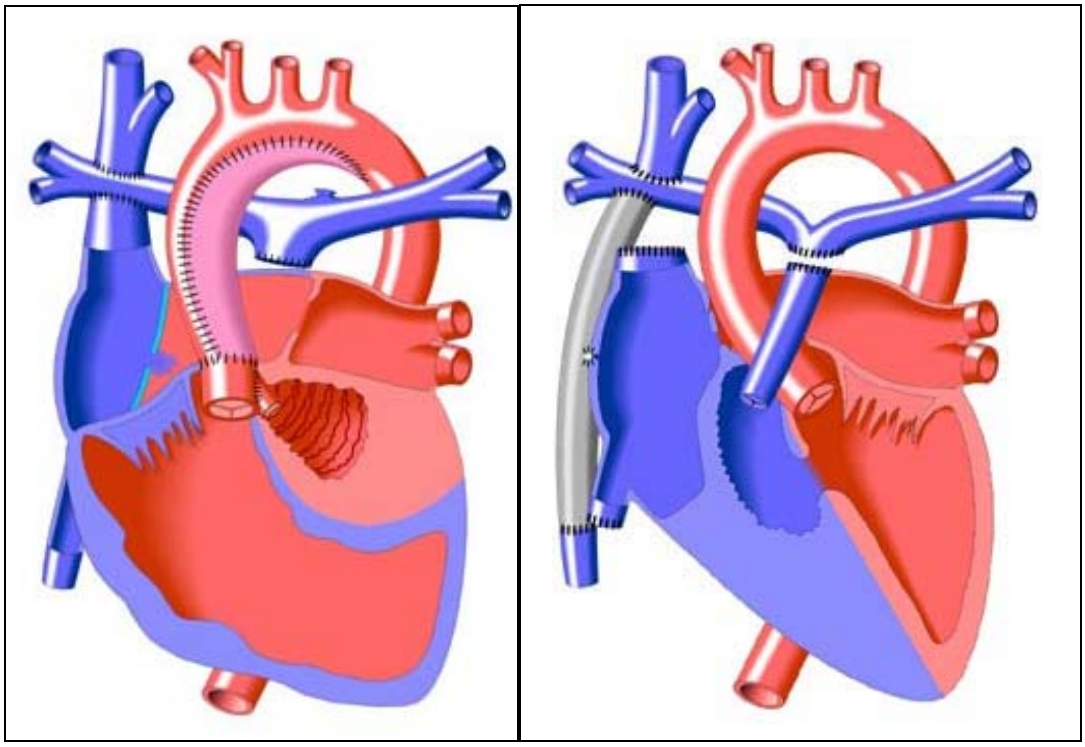

Figure 9: Lateral tunnel TCPC with hypoplastic left heart syndrome (left). Extracardiac conduit TCPC in a patient with tricuspid atresia and hypoplastic right heart (right)

Since the early 90's children were treated with a new approach. Normally it is structured in three surgical steps during the first two years of life. The advance to the classic Fontan is a better hemodynamic condition causing lower incidences of obstructions of the cavopulmonary pathway and less arrhythmia because of the absence of atrial dilation. This prolongs not only survival, but rather provides an improved quality of life and less diminished exercise performance in comparison the patients who had undergone a classic Fontan procedure.[25, 44, 47]

Finally, same as with patients with TGA, there is a large cohort of adults alive who underwent the classic Fontan procedure in their childhood. Those should be under special surveillance and a possible conversion to a TCPC should be carefully discussed.

3.9. Complex Cyanotic Congenital Heart Disease

Advancements in the treatment of CHD is the result of why many patients with cyanotic CHD at birth can now be surgically corrected in infancy or early childhood to a normal azyonotic circulation (e.g. ToF, TGA). Those patients with

reputed CHD like isolated shunts nowadays, receives attention earlier in life avoiding the development of pulmonary hypertension resulting in shunt reversal such as Eisenmenger syndrome[35, 122] (ES) which is a common reason for acquired cyanotic CHD later in life (Figure 10).

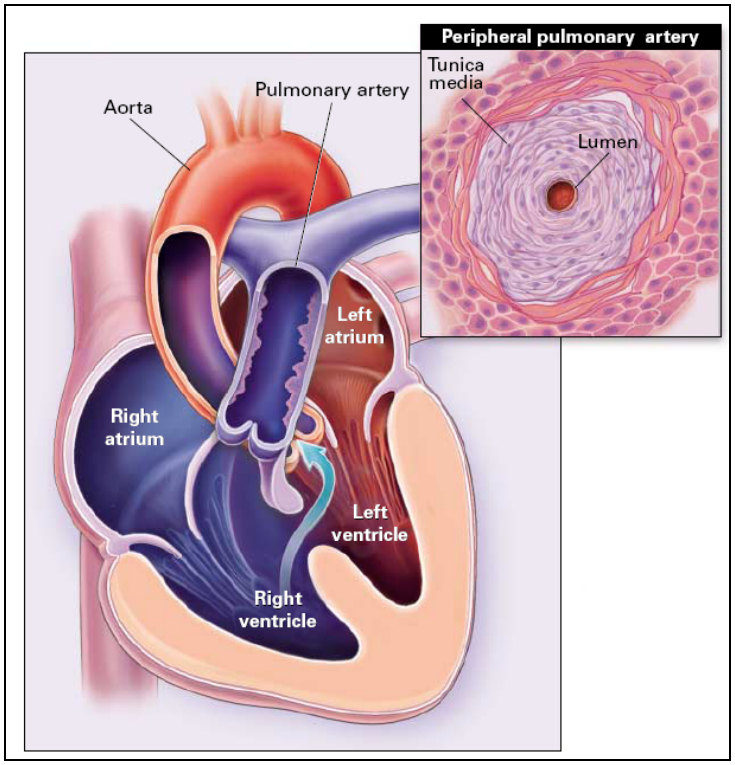

Figure 10: Eisenmenger Syndrome with right-to-left shunt

Nevertheless, there are several patients with cyanotic CHD who had no surgical management such as hypoplastic pulmonary arteries or their tremendous underlying complexity in remarkably stable situation.

Their survival depends mainly on the balance of pulmonary to systemic blood flow. If pulmonary blood flow is unrestricted, patients suffer from heart failure beginning in infancy after the natural decline of pulmonary vascular resistance, until they develop pulmonary vascular disease resulting in ES. On the other hand, if any kind of pulmonary stenosis is too extensive, they become severely cyanotic. Survival is best with a balanced pulmonary blood flow. This situation is either achieved by a moderate PS, genuine or after pulmonary arterial banding, or by increased pulmonary vascular resistance in ES.[53, 79]

Regrettably, during exercise, when systemic vascular resistance drops, pulmonary blood flow decreases and cyanosis becomes severe. It is for this

reason that exercise capacity and quality of life is at its worse in the cohort of patients with CHD.[30, 31, 79, 111]

Targets of clinical management are cyanosis, arrhythmia, thromboembolism and heart failure.[29, 31] However, treatment options are generally limited to palliative measures, drugs for the treatment of pulmonary hypertension and very selected subgroups of patients may be considered for heart–lung transplantation.[29]

3.10. Uncommon Congenital Heart Disease

In addition to table 1, there are more various diagnoses and subgroups of CHD such as cardiomyopathies, channelopathies, congenital corrected transposition of the great arteries or patients with truncus arteriosus communis. However, their prevalence is regrettably too small to seek statistical relevance in a single centre approach. Thus, for statistics, they are clustered in a separate group ("Other").

4. Methods

4.1. Quality of Life Assessment

To assess depression and health-related quality of life, standardized and well evaluated questionnaires were used. The patients received two questionnaires at the beginning of the investigation and had to complete them without any help. Those lacking reading ability or those cognitively unable to fill in the questionnaire without any help were refrained from participation.

4.1.1. Medical Outcomes Study 36 Item Short Form (SF-36)

Patients' quality of life was assessed by the medical outcomes study 36 item short form (SF-36). A generic measure of health status or health related quality of life, evaluated and used in various specialities of medicine and not specific for symptoms of any disease were used. It was also intended for use in international studies, as multiple translations were available and their comparability has been tested.

This instrument consisted of 36 questions that can be answered in about 5 minutes by ticking one of 3–6 given answers. It is a multidimensional instrument with eight multi-item components assessing physical functioning (the extent to which health limits daily physical activities), role functioning-physical (the extent of which physical health interferes with work or other daily activities), bodily pain (the extent of bodily pain and its effect on daily life), general health perception, vitality, social functioning (the extent to which health interferes with social activities), role functioning-emotional (the extent to which emotional problems interfere with daily activities), and mental health (a rough score for depression, affect, anxiety, etc). A single item component assessed health transition (health changes in the past year).

The score of each component was converted to scales from 0–100 with higher scores representing a better quality of life. The self reporting questionnaire with a window of four weeks in the German translation with the corresponding reference values from Bullinger et al. is used.[15, 16]

4.1.2. Allgemeine Depressionsskala (ADS)

To assess depression, the German translation of the “Center for Epidemiologic Studies Depression Scale” from Radloff named “Allgemeine Depressionsskala” (ADS) is used.[90]

It was designed to measure self-reported symptoms associated with depression experienced in the past week. The ASD has been proven to be a reliable measure for assessing the number, types, and duration of depressive symptoms across racial, gender, and age categories.[62, 90, 93]

The long form consists of 20 items retrieving depressive symptoms like depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance. With four possible responses to each question, patients report on presence and expression of symptoms over the last 7 days. Symptoms were summed up. A score of 0 represented no depressive symptoms and a score of 60 stated a maximal symptomatology.

According to the German evaluation study[55] from Hautzinger & Bailer, individual values were summed up and depression was defined as a score higher than 23. For a reliable response, the questionnaire contains a “lying score” and patients with this score lower than -27 were refrained from statistical analysis.[55]

4.2. Cardiopulmonary Exercise Test (CPET)

All patients underwent a symptom limited cardiopulmonary exercise test on a bicycle in upright position according to the American College of Cardiology and American Heart Association guidelines of 2002.[48, 118]

After a 3-minute rest to define baseline values, patients had a 3-minute warm-up without load, followed by a ramp-wise increase of load with 5, 10, 15, 20 or 30 W/min depending on the expected individual physical capacity estimated by the investigator. The aim was to reach a cycling time of about 8 to 12 minutes after warm-up. The end of the CPET was marked by symptom limitation and was followed by a 5-minute recovery period, with the first 2-3 minutes cycling with minimal load.

The exercise test featured a breath by breath gas exchange analysis using a metabolic chart (Vmax 229, SensorMedics, Viasys Healthcare, Yorba Linda, California). Peak $\dot{V}O_2$ was defined as the highest mean uptake of any 30 second time interval during exercise.

Reference values (ml/kg/min) were calculated for those 18 years and older according to Cooper and Storer.[22]

female: $\dot{V}O_2$ peak = 5.8 + (62.6 • height(m) – 45.5) • (37.03-0.371 • age(years)) / weight(kg)

male: $\dot{V}O_2$ peak = 5.8 + (71.6 • height(m) – 51.8) • (44.22-0.394 • age(years)) / weight(kg)

For patients 12-17 years old, reference values (ml/kg/min) were calculated according to Cooper.[23]

female: $\dot{V}O_2$ peak = (22.5 • height(cm) – 1837.8) / weight(kg)

male: $\dot{V}O_2$ peak = (43.6 • height(cm) – 4547.1) / weight(kg)

For patients younger then 12 years, the pooled data from both sexes were used:

$\dot{V}O_2$ peak = (37.1 • height(cm) – 3770.6) / weight(kg)

4.3. Daily Activity Assessment

Daily physical activity was measured by the triaxial accelerometer RT3 (Stayhealthy, Monrovia, California, USA) over the next seven days after the examination.

The RT3 is designed as a complete activity recording and measurement system for clinical and research applications. Worn on the waist over seven consecutive days, it continuously tracks activities throughout the day with the use of piezo-electric accelerometer technology that measures motion in three dimensions and provides tri-axial vector data in activity units. It is only during showering or swimming and during bedtime that the accelerometer was taken off.

In the scientific research, vector magnitudes were used to calculate the three dimensions with a sampling epoch of one minute. Daily activity was defined as the mean value of activity units over these three days. The daily minutes in moderate (3-6 METs) and vigorous activity (>6 METs) were calculated, using the published cut-off-points for moderate (> 970 count/min) and vigorous (>

2333 counts/min) activity.[95] For statistics, the pooled data from moderate to vigorous activity representing all activity >3 METs were used.

According to the contemporary recommendation of the Centre for Disease Control and Prevention (CDC), for the average healthy adult to maintain health and reduce the risk for chronic disease, the amount of activity should be 30 minutes a day.[87] Recommendation for patients younger than 18 years was 60 minutes of moderate to vigorous activity per day according to Centre for Disease Control and Pate at al..[86]

4.4. Statistical Methods

For skewed data, all descriptive data were expressed in median values and interquartile ranges (Q1-Q3).

Non-parametric Mann-Whitney-U tests were calculated to find differences between two diagnostic subgroups. Non-parametric Wilcoxon tests were used to compare patients' data with their individual reference values. Comparisons in-between diagnostic subgroups were calculated using a Kruskal-Wallis test. Non-parametric Spearmen correlation was applied to find associations between the different outcome parameters.

Since data was normally distributed in research Chapter 5.4., descriptive data was expressed in mean values ± standard deviation. The Pearson correlation was used to find associations between daily activity, exercise capacity and quality of life data. Intra-individual differences in activity according to the day of the week were tested with a multivariate analysis of variance for repeated measurements (MANOVA).

All analyses were performed using PASW Statistics 17.0 (SPSS Inc, Chicago, Illinois, USA). P-values <0.05 in a two-sided analysis were considered significant. If more variables are tested p-value was adjusted according to Bonferroni.

5. Study Results and Discussion

5.1. Exercise capacity, quality of life and daily activity in the long-term follow-up of patients with univentricular heart and total cavopulmonary connection (TCPC)[77]

Aim of the study

The objective of the study was to gain insight into the activity patterns of patients after TCPC and to determine the different factors on which daily activity might depend.

Study subjects

We investigated patients that had undergone a TCPC in our institution before 2002. Patients with an earlier Fontan modification converted to a TCPC were excluded from the study (Figure 11).

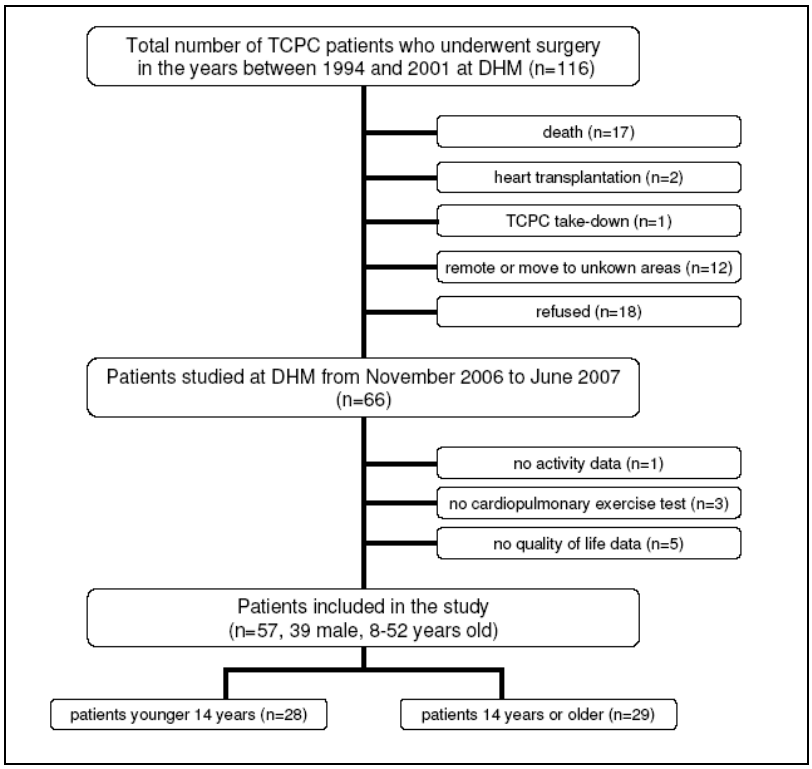

Figure 11: Patients inclusion.

Of 116 eligible patients 17 patients died during follow-up, two had heart transplantation and one required a take-down operation. Another 12 moved to remote or unknown areas and 18 patients refused to be studied.

From the total number of 66 patients recruited to our study and examined from Oktober 2006 to June 2007, one patient refused to wear the accelerometer, three were not able to perform a symptom-limited exercise test due to motoric handicaps and another five patients could not fill out the quality of life questionnaire (in two for language barriers, in three for mental retardation). So, 57 patients between 8 and 52 years old completed the whole protocol and were included in the study.

Twenty-one patients had a double inlet left ventricle, 15 tricuspid atresia, eleven hypoplastic left heart syndrome, five hypoplastic right heart syndrome, three double outlet right ventricle with imbalanced ventricles and two an complete atrioventricular septal defect with imbalanced ventricles. Heterotaxy was present in three patients.

Medication consists of oral anticoagulation (53 patients), ACE inhibitor (25), diuretics (8), beta-blocker (3) and digoxin (2).

In 28 patients a lateral tunnel and in 29 patients an extra-cardiac conduit was performed in between 1994 and 2001. Median age of the patients at follow-up was 14.0 (interquartile range 11.0-17.8 years). TCPC was completed with a median age of 5.6 (3.7-8.4) years. In 56% (n=32) of the patients a partial cavopulmonary connection (PCPC) was preceding the TCPC. A fenestration was created at surgery in 42% (n=24) of the patients with only 4 fenestrations open at follow-up.

Three patients suffered from intermittent or persistent protein-losing enteropathy with a total protein level in serum of less than 5.5 g/dl.

NT-proBNP was within the normal range of less than 480 ng/l in all, but four patients.

The study was in accordance with the declaration of Helsinki (revision 2008). The study protocol was approved by the local ethical board (project number 1568/06). All patients gave written informed consent.

Results

Exercise capacity

Median peak $\dot{V}O_2$ was 25.0 ml/min/kg (20.6-28.7 ml/min/kg) corresponding to 59.7 % (51-69%) of the age and sex related reference values.

In children less than 14, exercise capacity was estimated to 62.1% (56.6-73.9%) of age and sex related reference values, in the teenager and adult group mean percentage of relative peak $\dot{V}O_2$ was slightly lower with 56.0% (47.7-65.5%) of the reference value, outlining that even age and sex corrected peak $\dot{V}O_2$ decreased with advancing age (Spearman r=-0.339, p=0.010). A closer look to the data revealed that especially in males there was not the usual increase of exercise capacity during puberty, but rather a progressive decline from early adolescence on (Figure 12).

Exercise capacity was related to NT-proBNP (Spearmen r=-0.322, p=0.017). However, we failed to find relations to systemic ventricular morphology, type of TCPC, fenestration and protein-losing enteropathy. Exercise cyanosis, defined as oxygen saturation below 85 percent during exercise, was observed in twelve patients.

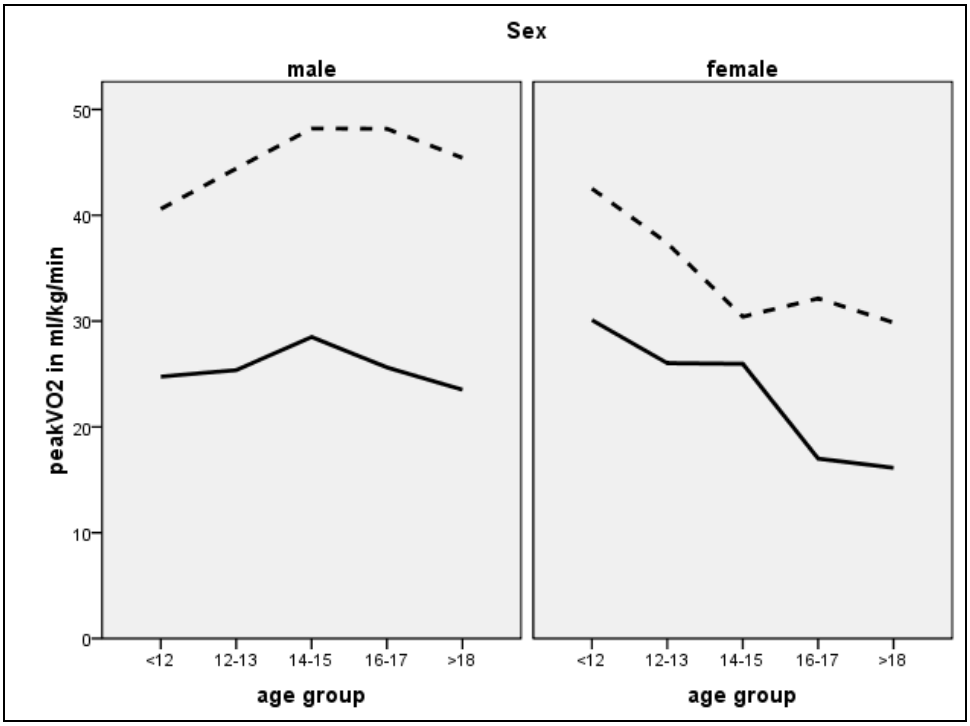

Figure 12: Exercise capacity according to age, median measured values (full lines) are compared to the median of the individual reference values (dashed lines), depicting that in males there is no pubertal increase in exercise capacity and in females there is an enhanced decline of exercise capacity starting already in childhood.

Quality of life

Self estimated quality of life was fairly good. In many scales the best imaginable result was achieved in many patients (Table 2).

CHQ-87 (younger than 14 years)		SF-36 (14 years or older)	
Dimension	**Median (Q1-Q3)**	**Dimension**	**Median (Q1-Q3)**
Physical functioning	92 (85-96)	Physical function	85 (62.5-91)
Role-emotional	100 (100-100)	Role-physical	100 (75-100)
Role-behavioural	100 (100-100)	Bodily pain	100 (74-100)
Role-physical	100 (92-100)	General health	77 (64-81)
Bodily pain	100 (73-100)	Vitality	65 (52.5-75)
General behaviour	87 (78-92)	Social function	100 (87-100)
Mental health	78 (71-89)	Role-emotional	100 (100-100)
Self esteem	84 (77-93)	Mental health	76 (72-86)
General health	62 (53-73)		
Family activities	90 (83-99)		
Family cohesion	85 (85-100)		

Table 2: Health related quality of life of children < 14 years (CHQ-87) and adolescents/adults 14-52 years (SF-36) with univentricular heart after total cavopulmonary connection

Daily activity

From 57 data samples, median moderate activity was estimated to be 87 minutes per day (48-112 minutes) and 12 minutes per day (6-24.5 minutes) spent in vigorous activity. The pooled data of these two activity intensities were 98 minutes per day (53-135 minutes). Daily activity was within the recommendations of the United Kingdom Expert Consensus Group (≥ 60 minutes, ≥ 3 MET, ≥ 5 days/week) in 41 patients (72% of the investigated patients) (Figure 13).

Time spent in moderate and vigorous activity correlated significantly with age (Spearmen r=-0.506, p<0.001) and exercise capacity expressed as percentage of expected (Spearmen r=0.432, p=0.001), representing decreased activity with

proceeding age and decreasing exercise capacity. No significant differences between males or females were found.

In the subgroup of children aged younger than 14 the mean activity was 119 min/day (77-178 minutes, n=28) showing an inverse correlation only to age (Spearmen r=-0.451, p=0.016). Patients who were 14 years or older achieved 73 min/day mean activity (43-118 minutes, n=29) per day with a moderate relationship only to exercise capacity (Spearmen r=0.477, p=0.009).

Neither surgical parameter (extra-cardiac or lateral tunnel TCPC, fenestration, prior partial cavopulmonary connection), nor other signs of a failing Fontan circulation (protein-losing enteropathy, NT-proBNP) showed any relationship to daily activity.

Only in the children's group a significant, but weak correlation to the Mental Health subscale (Spearmen r=0.380, p=0.046) representing anxiety and depressing in the CHQ-87 instrument could be detected. No other relation of any scale of the quality of life questionnaires could be found with daily activity in our TCPC cohort, even not to vitality or physical functioning.

Furthermore, seasonal effects in the study period for a higher activity in the months at spring were only small and failed significance (Kruskal-Wallis X^2=13.9, p=0.085).

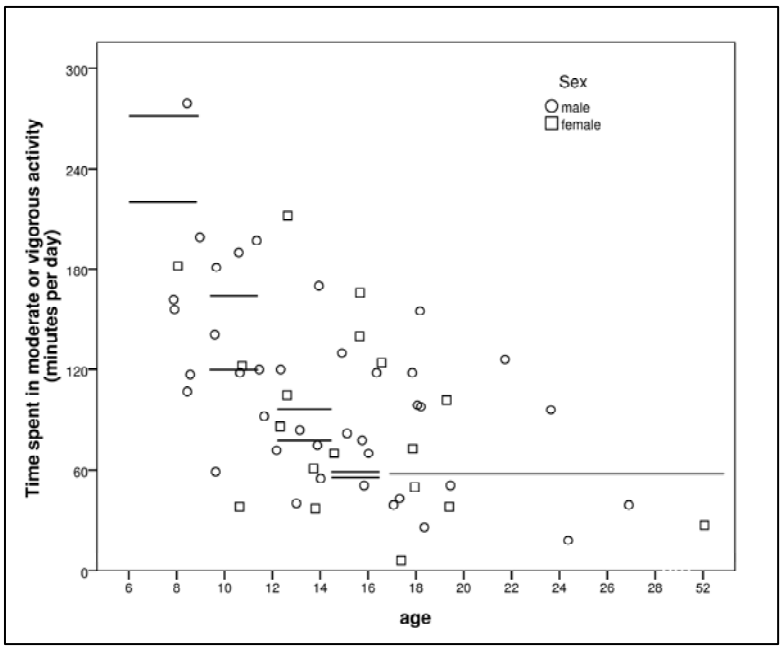

Figure 13: Daily time spent in moderate or vigorous physical activity for each TCPC patient by patient age for males and females. Reference lines are the age group 50th percentiles for normal, healthy children according to Pate and > 17 years of age the recommendations for physical activity according to the United Kingdom Expert Consensus Group.

Discussion

Exercise capacity

This study shows a substantial reduction of exercise capacity, measured as peak $\dot{V}O_2$ in a cardiopulmonary exercise test, in the TCPC patients. These findings are in concordance with previous studies that have reported exercise limitations in patients with diverse congenital heart disease[30, 50] as well as in Fontan patients.[46, 73] Like in the longitudinal study of Giardini and colleagues[46] we found a decrease of peak $\dot{V}O_2$ in adults over the years even compared to the normal decline in healthy subjects. Additionally to this disproportionate decline with proceeding age, the gender analysis in our study revealed that there was no increase of peak oxygen uptake during puberty in males. This is in contrast to healthy male adolescents who increase muscle mass substantially during puberty. In our patient group exercise capacity stayed unchanged during childhood and declined from early adolescence on.

Furthermore, we speculated on a better exercise performance in the extra-cardiac conduit subgroup. Up to now, only electrophysiologic variables could show a clinical advantage of an extra-cardiac conduit over a lateral tunnel TCPC.[2, 28, 85] We also failed to find any differences in exercise capacity. However, our extra-cardiac TCPC patients were slightly older at TCPC and at follow-up than our lateral tunnel TCPC patients making a realistic comparison impossible.

Daily activity

Nevertheless, our study showed a fairly normal daily activity pattern in our TCPC patients. According to the recommendations of the United Kingdom Expert Consensus Group, our patient group after total cavopulmonary connection mostly complied with the standards for daily activity in moderate (87 minutes/day) and vigorous (12 minutes/day) exercise. In only 16 of our 57 patients (28%) a functional reduction of daily activity, missing the recommended 60 minutes a day, was noted. Therefore, our group of TCPC patients was substantially more active than the congenital heart disease groups of McCrindle and Massin, who reported reduced physical activity patterns in Fontan patients[73] and patients after arterial switch operation.[72] Compared to

McCrindle's all-kind-of-Fontan group, we speculate that the main factor for increased physical activity in our cohort was the better hemodynamic situation of the TCPC, representing the contemporary standard of surgical treatment in univentricular hearts and outperforming the long-term results of other Fontan procedures like atriopulmonary connection or atrioventricular connection.[46]

Another factor for increased daily activity might be the changing aftercare philosophy of our department within the last five years. Exercise and sport was not categorically discouraged. On the contrary, we encourage our patients after a solid checkup to attend at school sports and moderate exercise.

In agreement with other studies in healthy children[86, 96] as well as in Fontan patients[73], we observed a strong age-related decline in physical activity. Only a closer look to the individual activity data revealed, that the lack of physical activity compared to healthy pears is most prominent in the youngest age group below nine, when physical activity in healthy children seems to be most liberate throughout life. Overprotection has been reported as an important issue for exercise limitation in the younger patients with congenital heart disease.[92] It is not astonishing that, in accordance to McCrindle[73], the youngest children are furthest away with regard to daily activity from their healthy counterparts. They are usually under close control of their parents and kept away from different type of sports and thus controlling their activity even with their exercise capacity being closest to normal in this life span.[46] Teenagers aged twelve to sixteen were less active, but nearer to norm values. With this age, we assume, they start to ignore the care from their parents and develop their own activity patterns.

In the adolescent and adult group of 14 years or older effects of aging diminished. In that age group there was clear coherence between daily activity and exercise capacity. This can be interpreted that only patients with a higher exercise capacity show a more active daily life. This might be a sign that indeed the reduced exercise capacity curtails the patients daily life despite they do not report that in health related quality of life questionnaires (present study,[50, 52]). In this older age group we speculate on this direction of the cause effect relationship, as exercise capacity is moderately to severely diminish whereas daily activity is close to normal. However, the reduced activity, especially the

reduced vigorous activity in early childhood, might be an important contributor for deconditioning and proper muscle build-up in childhood and puberty. This cause effect relationship, we propose in children, is supported by the fact, that none of the investigated variables of heart failure in Fontan patients, for example the incidence of sinus node dysfunction or protein-losing enteropathy, showed any relation to exercise capacity or daily activity

Daily activity and self-reported quality of life

In contrast to the patient group 14 years or older we only noted in the children subgroup a correlation between daily activity and mental health. This correlation outlines, that depression and probably more important anxiety transferred from overprotecting parents and health care provider to the young patients is an important reason for the diminished activity seen in that age group.

Furthermore, the lack of correlation between self-estimated vitality and objectively measured physical activity seems to be astonishing. However, these results are in concordance with McCrindle and colleagues[73] who reported only poor coherence in perceived general health and decreased physical activity patterns after Fontan operation. Other aspects of functional status, as well as the answers in a physical activity questionnaire did not show any correlation to measured daily activity in their study. Maybe this is the same phenomenon as previously reported by Hager et al.[52] and in a larger cohort by Gratz et al.[50] comparing objectively measured exercise capacity and self reported physical functioning of adults with congenital heart disease. They reported on a reasonable misinterpretation of the patients concerning their own physical capacity. Others also speculated about this misconception when comparing the results of direct psychological tests compared to the results of these subscales in self-reported quality of life instruments.

Study limitation

The measurement of daily activity over the next three consecutive days after examination was affected by weekday and weekend alteration. For future assessments of daily activity, recording over 1 week should be aspired.

Furthermore, the study period should be as small as possible to exclude seasonal effects.

The patients studied here represent a ‘positive’ selection of the total patient group of TCPC patients. The excluded patients could either not perform an exercise test or could not fill out a quality-of-life questionnaire, had heart transplantation or TCPC take-down, or even died during follow-up. So, we can only state that patients with a good result of their TCPC can achieve abnormal activity pattern in daily life despite severely diminished exercise capacity.

5.2. Exercise performance and quality of life is more impaired in Eisenmenger syndrome than in complex cyanotic congenital heart disease with pulmonary stenosis[79]

Aim of the study

We aimed to define differences from a single cardiopulmonary exercise test between the groups of patients with complex cyanotic congenital heart disease with pulmonary stenosis and patients with Eisenmenger syndrome and whether they are related to the quality of life.

Study subjects

We retrospectively analyzed all patients aged fourteen years or older with major intra cardiac right-to-left shunts, referred to our exercise laboratory as part of their routine follow-up, with progressive cyanosis under exercise. Patients with major aorto-pulmonary collateral arteries were excluded. All CPET were performed between October 2001 and February 2009.

In total fifty-eight patients (28 male, 30 female, aged 14-55 years) could be studied. Twenty-three of them had hemodynamic relevant pulmonary stenosis (PS) or pulmonary arterial banding (PAB). Anthropometric data are shown in Table 4. Diagnoses were Double Inlet Left Ventricle in nine patients, Transposition of the Great Arteries in five, Congenital Corrected Transposition of the Great Arteries with Ventricular Septal Defect in five, as well as Tricuspid Atresia, Pulmonary Atresia, Hypoplastic Left Heart Syndrome and Complete Atrioventricular Septal defect with unbalanced ventricles in one.

Thirty-five patients had Eisenmenger syndrome (ES). Twenty one of them had a Ventricular Septal Defect, nine Atrial Septal Defect and six Complete Atrioventricular Septal Defect. Sixteen Eisenmenger patients were treated with vasodilators (9 bosentan, 4 sildenafil, 2 sildenafil and bosentan, 1 sitaxentan).

The study was in accordance with the declaration of Helsinki (revision 2008). Patients agreed to the anonymous publication of their data.

Results

Cardiopulmonary exercise test

CPET could be performed even in these severely symptomatic patients without any incident. Ventilatory threshold could not be determined properly in 18 patients with ES and two patients with PS. Results are shown in Table 3.

Exercise capacity displayed as peak $\dot{V}O_2$ was severely reduced (13.0 ml/min/kg corresponding to 38.6% of age and sex related reference values) and ventilatory efficiency expressed as $\dot{V}_E/\dot{V}_{CO_2}$ slope was markedly increased, while $P_{ET}CO_2$ was diminished substantially.

Pulse oxymetric oxygen saturation (S_pO_2) was reduced at rest and decreased severely under exercise. However, S_pO_2 at rest was strongly correlated to peak $\dot{V}O_2$ (r=0.436; p=0.001) and $\dot{V}_E/\dot{V}_{CO_2}$ slope (r=-0.388; p=0.003). Moreover, patients with lower oxygen saturation at rest had higher hemoglobin level (r=-0.386; p=0.003).

Comparison of diagnostic subgroups

There were no significant differences between the two subgroups in hemoglobin levels, in pulse oxymetric oxygen saturation (S_pO_2) at rest, and in S_pO_2 under exercise.

However, there were significant differences in age in between the two subgroups. So CPET data were additionally expressed in % of age, body mass, height, and sex related reference values (Table 3).

Exercise capacity displayed in maximal oxygen consumption in ES was worse than in cyanotic patients with PS (p=0.044). Moreover, ventilatory efficiency expressed as $\dot{V}_E/\dot{V}_{CO_2}$ slope was more impaired in the ES group (p=0.005) and the y-intercept from the $\dot{V}_E/\dot{V}_{CO_2}$ curve was significant lower in ES (p=0.002). End-tidal $P_{ET}CO_2$, was reduced in both subgroups but without significant difference between the two subgroups (Table 3).

		Total $n=58$	Pulmonary stenosis $n=23$	Eisenmenger $n=35$	p-values*
		Median (Q1;Q3)	Median (Q1;Q3)	Median (Q1;Q3)	
Sex	Males/females	28/30	12/11	16/19	0.789
Age	Years	27.9 (22.2;35.7)	24.3 (19.9;26.4)	33.7 (27.1;37.2)	**4.1×10^{-4}**
Hemoglobin**	(g/dl)	19.5 (16.7;22.3)	18.2 (16.1;21.2)	20.5 (17.9;22.5)	0.121
SpO_2 saturation (%)	Rest	88.5 (80.5;93)	90.0 (84.0;93.0)	87.0 (77.0;93.0)	0.179
	VT***	76.5 (70.5;86.5)	74.0 (68;85.5)	77.0 (73.0;88.0)	0.399
	Peak	64.5 (55.3;75.5)	65.0 (59.0;77.0)	64.0 (47.0;75.0)	0.369
$\dot{V}_{O_2}$ (ml/min/kg)	Rest	4.4 (3.7;5.3)	4.6 (3.8;5.3)	4.2 (3.4;5.3)	0.294
	VT***	9.7 (7.9;12.1)	11.6 (9.5;15.4)	8.3 (7.0;9.9)	**0.002**
	Peak	13.0 (10.3;19.2)	20.3 (11.9;24.6)	11.3 (9.7;14.5)	**2.2×10^{-4}**
	% pred.	38.6 (29.3;48.1)	47.5 (30.0;64.5)	36.3 (29.1;43.3)	**0.044**
$P_{ET}CO_2$(mmHg)	Rest	26.5 (24.3;29.2)	26.8 (25.3;28.4)	26.3 (24.2;30.4)	0.905
	VT***	26.3 (24.6;30.5)	26.5 (25.0;30.0)	26.3 (23.9;31.0)	0.948
	Peak	23.2 (20.3;26.7)	23.0 (21.9;25.1)	23.6 (19.3;28.4)	0.805
$\dot{V}_E/\dot{V}_{CO_2}$	Rest	60.5 (53.0;70.5)	60.0 (52.0;65.0)	61.0 (54.0;76.0)	0.611
	VT*	52.0 (44.5;57.0)	49.5 (42.75;54.5)	55.5 (49.0;62.75)	0.057
	Peak	54.0 (48.75;62.0)	53.0 (48.0–60.0)	58.0 (49.0;65.0)	0.161
	Slope	47.2 (42.1;59.5)	45.7 (37.6;52.9)	54.6 (43.4;68.7)	**0.005**
	y-intercept	2.18 (0.01;3.21)	2.73 (2.32;4.42)	1.37 (−0.35;2.25)	**0.002**
RER	Peak	0.99 (0.93;1.08)	1.04 (0.96;1.13)	0.97 (0.92;1.04)	0.056

Table 3: Anthropometric data and CPET variables according to diagnostic groups compared with a two-sided Mann-Whitney-U test (*).

** In one patient hemoglobin levels were not available

*** As VT could not be determined properly in all patients VT data are limited to 21 patients with PS and 17 patients with ES

Quality of life

Quality of life measurement was available in only 43 patients (21 PS, 22 ES). Fifteen patients (2 PS, 13 ES) were cognitively not able to fill in the quality of life questionnaire. Results and p-values of self estimated quality of life were displayed in Table 4.

Self estimated quality of life was significantly reduced in physical functioning, role physical, general health, and vitality in correlation to peak $\dot{V}O_2$ and $\dot{V}_E/\dot{V}_{CO_2}$ slope, but not in correlation to S_pO_2. The other, more mental components showed no differences to the reference values.

When comparing the PS and the ES group, all median values of the nine dimensions were lower in the ES group. However, significance was reached only in physical und social functioning (Table 4).

Dimension	Total $n=43$	Pulmonary stenosis $n=21$	Eisenmenger $n=22$	p-values*
	Median (Q1;Q3)	Median (Q1;Q3)	Median (Q1;Q3)	
Physical function	55 (40;70)**	60.0 (52.5;85.0)	45.0 (33.75;57.5)	**0.013**
Role physical	100 (25;100)**	100 (75;100)	50 (0;100)	0.060
Bodily pain	100 (62;100)	100 (100;100)	92 (56.75;100)	0.213
General health	55 (42;67)**	62 (47;72)	52 (41.5;62)	0.362
Vitality	55 (45;75)**	55 (47.5;77.5)	52.5 (33.75;71.25)	0.511
Social function	100 (75;100)	100 (87.5;100)	75 (50;100)	**0.049**
Role emotional	100 (66.7;100)	100 (100;100)	100 (33.33;100)	0.435
Mental health	76 (64;80)	76 (68;86)	68 (54;77)	0.052
Health transition	50 (50;50)	50 (37.5;50)	50 (43.75;75)	0.227

Table 4: Median and interquartile range of self estimated health related quality of life in the Eisenmenger Group compared to the pulmonary stenosis group.

* two-sided Mann-Whitney-U test calculated with % predicted

** significantly reduced (two-sided Wilcoxon test with reference value) in physical functioning (p=1.1E-8), role physical (p=0.018), general health (p=6.7E-8), and vitality (p=0.003)

Discussion

This study showed that patients with cyanotic congenital heart diseases have a severely diminished exercise capacity, ineffective ventilation at rest that even worsens under exercise. Furthermore, they have a curtailed quality of life predominantly in the physical domains. Pulse oxymetric oxygen saturation at rest seems to predict exercise capacity and the functional status of patients in this study cohort, but not quality of life.

In most of the investigated criteria, patients with Eisenmenger syndrome showed even worse results than patients with cyanotic congenital heart disease with pulmonary stenosis.

Safety of exercise testing

There were no incidents at exercise testing even in that severely cyanotic patient group. In concordance with others[49], this confirms our policy, to perform exercise tests also in severely cyanotic patients, even when S_pO_2 drops below 70%, where pulse oxymetry is no longer reliable. However, we always stop the exercise test at once when the cyanotic patient starts to complain any symptoms that might be referred to cerebral malperfusion or ischemia even if criteria of metabolic exhaustion like a respiratory exchange rate >1.1 or reaching a plateau in oxygen uptake are not met. In this context it is very important to choose an appropriate exercise protocol that does not overstress the patients at the beginning and does not provoke inconvenience in the patient.

Exercise capacity

It is well established, that patients with congenital heart disease show diminished exercise capacity that increases with the severity of the underlying defect.[30, 41, 49, 51, 111] Diller et al. showed that peak $\dot{V}O_2$ is a powerful predictor of mortality in patients with congenital heart disease[30]. A peak $\dot{V}O_2$ of 15.5 ml/kg/min was a predictor for mortality in that group combining several congenital defects. In our study only 7 (20%) of the ES patients but 15 (65%) patients with PS reached this threshold. In concordance to Diller et al.[30] and Trojnarska et al.[110, 111] our study showed the tremendous reduction of peak $\dot{V}O_2$ in patients with persistent cyanotic congenital heart disease. Such as in these

two studies the reduction in peak $\dot{V}O_2$ was more prominent in patients with ES than in cyanotic patients with PS.[30, 111] Notwithstanding, there was a mean difference in age in-between the two subgroups, what might weakens the comparison of exercise capacity. Exercise consumption decreases steeper in Fontan patients, which is also a subgroup of congenital heart defects with severely limited exercise capacity, than in normal population.[47] However, the normal decline over a decade is about 10% in healthy people and about 30% in Fontan patients. We do not think that a steeper decline of peak $\dot{V}O_2$ alone accounts for our 45% difference in absolute peak $\dot{V}O_2$ values between the two subgroups that differ about one decade in age.

However, as already mentioned as safety issue, CPET to maximum exhaustion to assess exercise capacity has important limitations. In our patient groups a plateau is rarely reached at peak exercise[84] due to muscular exhaustion of the legs or the feeling of discomfort in the severely cyanotic patient.[20] This discomfort cannot be differentiated whether it is a first neurological sign or simply a lack of motivation. Also other signs of full metabolic exhaustion are rarely achieved as symptoms in this cohort as fatigue, dyspnoea and dramatically cyanosis proceed under exercise. Therefore, we can not state that measured peak $\dot{V}O_2$ really resembled metabolic max $\dot{V}O_2$. However, the measured peak $\dot{V}O_2$ is the maximum the patient reached when they forced themselves to exercise as far as it seemed to be acceptable for themselves and for the supervising physician. In the comparison between the two groups there was a slight trend to a lower respiratory exchange ratio at peak exercise in the ES. This might be due to the fact that most of the patients with ES fear exercising as they are refrained from any kind of physical activity as recommended for patients with pulmonary arterial hypertension without shunt to prevent syncope from right heart failure.

In patients without any shunt, the anaerobic threshold was suggested to provide an reliable submaximal parameter for cardiac patients to overcome the need of complete exhaustion to determine max $\dot{V}O_2$. However the increasing right-to-left shunt during exercise show effects on the $\dot{V}O_2$ - $\dot{V}CO_2$ - $\dot{V}E$ relation[105] that often hampers the exact non-invasive determination of the ventilatory threshold.

In accordance with Gläser et al.[49] we think that this submaximal parameter is of less value in cyanotic patients.

Pulse oxymetric oxygen saturation (S_pO_2)

Oxygen saturation was severely reduced in this cohort. Same like Diller et al.[29] we found an inverse correlation between hemoglobin levels and oxygen saturation at rest. However, neither hemoglobin levels nor oxygen saturation showed any differences in-between the diagnostic groups during rest, ventilatory threshold or peak exercise.

In contrast to Gläser et al.[49] oxygen saturation measured at rest was associated with peak $\dot{V}O_2$ and $\dot{V}_E/\dot{V}_{CO_2}$ slope, stating beneficial results to patients with higher S_pO_2 at rest. As reported in drug studies with endothelin receptor antagonism,[74, 99] an increase in S_pO_2 at rest results in a higher exercise capacity or prolonged 6-minute walking distance. Thus, S_pO_2 at rest is an important parameter not only for ES, but also for patients with cyanotic congenital heart disease to quantify the functional status of the patient and to predict exercise capacity. From hemodynamic point of view, a reduced pulmonary blood flow with cyanosis limits exercise capacity more than an increased pulmonary blood flow at rest with higher cardiac volume load.

Ventilatory inefficiency

To overcome methodological limitation of peak exercise parameter we focused on ventilatory efficiency as a powerful sub-maximal parameter. Thereby, the linear relation between carbon dioxide output ($\dot{V}_{CO_2}$) and minute ventilation ($\dot{V}_E$) during CPET is used to describe the ventilatory response to exercise expressed as $\dot{V}_E/\dot{V}_{CO_2}$ slope.[19] It is fairly independent from the patients' motivation as the relation between $\dot{V}_E/\dot{V}_{CO_2}$ is linear from the beginning of the exercise test on.[19, 119] Steeper slopes represent a pulmonary ventilation/perfusion mismatch. This is the result either by a real ventilation or perfusion problem, but also due to increased dead space ventilation at extraordinary hyperventilation[19, 104] caused by acidosis, CO_2-shunting or enhanced ergoreceptor reflex. It is associated with poor exercise capacity[19, 21, 31] and limited survival[31] in patients with heart failure[19, 21] and with congenital heart disease.[45, 111]

Confirming Dimopoulus et al.[31] and Trojnarska et al.[110] we found an abnormal $\dot{V}_E/\dot{V}_{CO_2}$ slope across all our patients. This is explained by the right to left shunt which is increasing at exercise. The shunting desoxyhemoglobin and especially the shunting CO_2 cause an excessive ventilatory drive at the carotid chemoreceptors at exercise. This hyperventilation increases the functional dead space ventilation whereas perfusion is not raised adequately because the shunt bypasses the pulmonary circulation.[105] Furthermore, it has to be assumed that an increased ergoreceptor reflex enhances this hyperventilation especially in those patients suffering from cardiac cachexia.

Similar to the aforementioned studies[31, 110] patients with ES had a significant higher $\dot{V}_E/\dot{V}_{CO_2}$ slope than the cyanotic patients with cardiac shunts protected from PAH by PS. Shunting measured as S_pO_2 decline at exercise is similar in both groups. The additional limitations in ES measured as peak $\dot{V}O_2$ and elevated $\dot{V}_E/\dot{V}_{CO_2}$ slope could be explained by a more inhomogeneous lung perfusion seen in the ES patients. In contrast, patients in whom the pulmonary vasculature is protected from pulmonary vascular remodelling by a PS seem to have a less affected lung ventilation/perfusion mismatch and are at least slightly able to improve ventilation/perfusion mismatch at the beginning of the exercise.

To confirm this hypothesis, we also focused on end-tidal CO_2 during CPET. In healthy people there is an increase of $P_{ET}CO_2$ under exercise till the respiratory compensation point and then a progressive decline till exhaustion.[121] In patients with major cardiac shunts or large ventilation/perfusion mismatch there are low $P_{ET}CO_2$ values at rest that further decline from the beginning of the exercise test on.[120] This could be shown in our total patient group of cyanotic patients. However, we failed to detect differences between the two investigated groups.

Furthermore we depicted the intercepts from the different $\dot{V}_E/\dot{V}_{CO_2}$ curves. An positive intercept causes the $\dot{V}_E/\dot{V}_{CO_2}$ to decrease with increasing work rates how it is observed in healthy people.[26] An intercept equal to zero inversely means that $\dot{V}_E/\dot{V}_{CO_2}$ won't decrease with increasing work load at the beginning of exercise. This phenomenon is almost exclusively seen in PAH patients.

Quality of life

This study shows that quality of life is diminished mainly in the physical dimensions. This is in agreement with other studies that outline the rather good quality of life in the mental and social domains and the limitations especially in the physical domains in the overall group of congenital heart disease.[51, 52, 58, 94] However the comparison of PS and ES patients suggested that ES patients are leaving the path of full mental health and compensated social life. This is underlined by the fact, that rather many ES patients have to be excluded from the SF-36 questionnaire due to cognitive limitations. This uncovers the real cognitive status of some patients especially in the ES group. The significantly worse self-estimated quality of life in ES patients in some domains outline that ES with all its additional burden on cardiovascular and other organ function has an overwhelming impact on almost all domains of life quality. This is in accordance with Lane et al.[66] and Popelova et al.,[89] who found a significant poorer quality of life in all scales of the SF-36 except in “emotional role” and a high incidence of depression in cyanotic patients.

Furthermore, it is this rather good quality of life in patients with cyanotic univentricular hearts, pulmonary stenosis and normal pulmonary vascular resistance that retards patients not to undergo transformation in a Fontan-like hemodynamic. This operation has excellent results in childhood and early adolescence. However in adulthood, this operation has a high mortality and even with successful surgery, nobody can guarantee the patient a better clinical situation with a passive pulmonary perfusion.

Study limitation

The study group is small, making statistical analysis underpowered to detect subtle differences between the two groups. Especially in the quality of life statistic, as well as the relation to CPET variables, results had to be clarified by a larger cohort. Moreover, the median age difference of nearly ten years in the two subgroups might have affected the data as far as peak $\dot{V}O_2$ could have decreased steeper with age in these diagnostic groups than in the normal population.

5.3. Minor symptoms of depression in patients with congenital heart disease have a larger impact on quality of life than limited exercise capacity[80]

Aim of the study

Determine the prevalence of depression in the vast cohort of CHD and its impact on quality of life and exercise capacity.

Study subjects

From November 2007 to October 2009, 1684 patients were referred for a cardiopulmonary exercise test (CPET) to our laboratory owing to various clinical indications. First, we excluded 43 patients without a congenital heart defect. If patients were tested more than once, only the first test was included in the study. Patients under the age of 14 years were excluded, as the questionnaires are not evaluated for that age-group. Furthermore, some patients lacked reading ability, had language barrier or mental retardation, or were in a prolonged hospitalization in our institution and thus were refrained from participation. Forty-three patients refused their participation. After all, our study cohort consisted of 787 patients.

The study was prospectively designed and in accordance with the declaration of Helsinki (revision 2008). The study protocol was approved by the local ethical board (project number 1931/07). All patients gave written informed consent.

Results

Since there was an algorithm for the ADS questionnaire for a reliable response 20 samples were removed from statistical analyze due to a positive “lying score”, so that in total 767 samples were statistically analyzed. Anthropometric data for the whole group and according to 11 diagnostic groups are presented in table 5.

ADS score and depression

ADS score and the prevalence of depression according to diagnostic subgroups were presented in table 5. The patients' ADS scores were significant less than their individual reference value (Wilcoxon test, $p<0.001$). Symptoms of depression were found in 66 patients (8.6%). There were no significant differences in the ADS scores (% predicted) between the diagnostic subgroups (Kruskal-Wallis test, $p=0.195$).

Referenced ADS values in "% predicted" were displayed in table 6.

ADS score related to quality of life and exercise capacity

Quality of life and exercise results according to diagnostic groups were presented in table 6.

ADS score was correlated to all of the nine dimensions of the quality of life questionnaire. Especially to the psychosocial domains intermediate and in the case of "mental health" strong correlation was achieved.

However, the correlation between ADS score and peak VO_2 ($r=-0.164$, $p<0.001$) was rather poor. ADS score showed a better correlation to all dimensions of quality of life than peak VO_2, even to the SF-36 dimension of "physical functioning".

Discussion

This study outlined the excellent psychological status in the vast majority of patients with CHD also in the field of depression. Astonishingly, only in 8.6% of the patients depressive symptoms fulfilled the criteria of depression. However, these minor symptoms of depression were strongly correlated to quality of life especially to the psychosocial domains and clearly exceeded the impact of exercise capacity.

As mentioned above, the prevalence of depression was fairly low with 8.6%. At first glimpse we assumed the young median age of 25.6 years in our cohort might have reduced the total number of depressive patients. But even corrected for age and gender, lower scores persisted in patients with CHD. But a closer

view showed that our findings are in line with many other studies who reported on excellent psychological status, comparable to standard population.[38, 112, 114]

One reason for these results might be that children and adolescents with CHD receive more attention than others. The parents involve themselves in a more profound way and encourage their children to communicate their physical problems as well as their sorrows and fears. This may lead to close bonding making mental adjustment to the situation easier.[38] Moreover, it is also possible that patients are aware of physical restrictions but do not interpret them as affecting their life in a negative way, and may adapt to their disease.[102] This leads to coping strategies reported from Utens et al., that denial mechanisms and high achievement motivation possibly lead congenital heart disease patients to overrate their emotional states.[112] Furthermore, Utens et al.[113] reported on emotional and behavioural problems in children and adolescents between 10-18 years. But in their subsequent study adults with CHD obtained better scores than healthy peers. Thus they concluded, that these contrasting findings may indicate that childhood emotional problems do not persist into adulthood.[112, 113]

Differences between the diagnostic groups according to ADS score were considered to be not significant. Basically, almost all other studies confirming this result, that depression and/or quality of life status concerning psychosocial domains are independent or only marginally correlated to the underlying defect or “severity” of the CHD.[38, 51, 52, 64, 66, 76, 102, 107, 113] However, the most of these cited studies refers only to the simpler lesions.

Just a detailed view to the cyanotic subgroup might be warranted. Popelova et al.[89] reported on a high prevalence of depression in adults with CHD and persistent cyanosis. Also Bromberger et al.[13] found that emotional disorders were more prominent in patients with cyanotic defects and complex lesions. Looking at our descriptive data the prevalence of depression in the cyanotic group was highest with 13.5%. In general, patients with cyanotic CHD have a slightly diminished quality of life concerning psychosocial issues.[51, 64, 66] Hence, the subgroup of cyanotic patients might be at higher risk to develop this emotional disorder and has to be under special surveillance.

Objectively measured exercise capacity displayed as peak $\dot{V}O_2$ was only marginally affected by symptoms of depression. This is in accordance to earlier studies showing that there is no correlation of peak $\dot{V}O_2$ with the psychosocial scales of the SF-36 even in patients with severe lesions.[51, 52]

Comparing the impact of depressive symptoms versus exercise capacity on quality of life, we cardiologists have to realize that even in some patients with severely diminished cardiac performance measured as exercise capacity, this exercise capacity is the weaker confounder of quality of life than small shifts in the psychological status of the individual. Interestingly, even self-estimated "physical function" derived from SF-36 showed numerically less correlation to peak $\dot{V}O_2$ than to the ADS score. In our earlier studies published by Gratz et al.[51] and Hager & Hess[52] we speculated on the inconsistent prediction of self reported functional exercise capacity in patients with CHD. The current study showed a possible answer: there is the huge impact of rather small depressive symptoms on the self-estimated exercise capacity.

Nevertheless, our former conclusion is underlined: It is essential to assess functional capacity from objective exercise testing and not to rely on the patients' anamnestic reports or self-estimated questionnaires; and it is necessary to evaluate quality of life separately in addition to the cardiac function variables. However, it has to be mentioned that exercise capacity is related to survival in CHD.[30] Thus both exercise capacity and quality of life have to be independently the aim of medical management.

Study limitations

This study was performed only in patients receiving regular special surveillance for congenital heart disease in our tertiary centre. It has to be mentioned that it is standard care in our institution also to focus on psychological issues in all our patients. This is not only implemented by the passion of the nurses and medical doctors, but also by psychologists employed in the cardiology department to look after the psychosocial needs of our paediatric and adult patients with congenital heart disease. This might have biased the data towards a better psychological outcome in that study. However, the results support our policy.

Moreover, refraining patients with language barrier, lacking reading ability or mental retardation from participation may biased the date to a higher educational or socioeconomic status each in prevalence of depression and exercise testing.

Diagnosis	n	sex female/male	age median (Q1-Q3)	ADS sum score median (Q1-Q3)	individual reference value median (Q1-Q3)	depression prevalence n (percentage)
Cyanotic	37	22 / 15	31.9 (25.1 - 41.1)	10.0 (6.5 - 18.0)	14.7 (12.8 – 16.1)	5 (13.5%)
Fontan circulation	57	24 / 33	25.8 (20.5 - 31.3)	9.0 (4.0 - 15.0)	13.5 (12.9 – 16.1)	6 (10.5%)
TGA after atrial switch	74	32 / 42	27.6 (23.6 – 32.7)	8.0 (5.0 - 17.0)	13.5 (12.9 – 16.1)	6 (8.1%)
TGA no atrial switch	50	20 / 30	19.8 (16.4 - 33.2)	6.5 (4.0 - 13.25)	13.5 (12.9 – 15.6)	2 (4.0%)
Tetralogy of Fallot	136	65 / 71	29.9 (19.7 - 33.1)	8.0 (4.25 -15.0)	13.5 (12.9 – 16.1)	13 (9.6%)
Ebstein anomaly	38	26 / 12	35.0 (26.8 - 47.4)	10.0 (5.0 - 19.5)	14.7 (13.5 – 15.6)	4 (10.5%)
PS / PR	47	21 / 26	24.9 (19.4 - 30.6)	9.0 (5.0 - 13.0)	13.5 (12.9 – 15.6)	3 (6.4%)
Coarctation of the aorta	68	15 / 53	24.1 (18.6 - 34.0)	7.0 (3.25 - 12.75)	13.5 (12.9 – 13.5)	1 (1.5%)
Aortic stenosis	103	26 / 77	23.1 (18.1 - 28.9)	6.0 (3.0 - 12.0)	13.5 (12.9 – 14.4)	8 (7.8%)
Isolated shunt	90	57 / 33	26.4 (20.0 - 37.0)	9.0 (5.75 - 17.0)	14.7 (13.5 – 16.1)	11 (12.2%)
Other	67	36 / 31	21.6 (17.4 - 29.4)	9.0 (5.75 - 17.0)	14.7 (12.9 – 16.1)	7 (10.4%)
Total	767	344 / 423	25.6 (19.5 - 33.0)	8.0 (4.0. - 15.0)*	13.5 (12.9 – 16.1)*	66 (8.6%)

Table 5: ADS score and prevalence of depression according to diagnostic groups.
ADS score: sum score of depressive symptoms. A score >23 is compatible with the diagnosis of depression.
* Patients show less depressive symptoms than the reference population (Wilcoxon test, $p=4.11\times10^{-36}$)
Kruskall-Wallis test could not find any differences in ADS scores (% of predicted) between the diagnostic groups (p=0.195)

	n	Peak $\dot{V}O_2$	ADS	Physical function	Role physical	Bodily pain	General health	Vitality	Social function	Role emotional	Mental health	Health transition
Cyanotic	37	42 (35-54)	73 (40-124)	67 (57-85)	109 (84-114)	114 (77-119)	72 (58-83)	88 (73-108)	96 (81-112)	108 (106-110)	101 (85-117)	96 (93-100)
Fontan circulation	58	59 (50-71)	61 (26-118)	94 (76-99)	104 (102-113)	112 (95-112)	91 (69-108)	93 (67-114)	107 (84-109)	106 (105-110)	110 (90-122)	94 (94-99)
TGA after atrial switch	78	68 (53-75)	62 (34-113)	96 (85-104)	102 (104-112)	112 (89-119)	93 (69-107)	96 (69-116)	107 (97-109)	107 (106-110)	104 (88-117)	95 (94-99)
TGA no atrial switch	52	75 (59-85)	48 (30-88)	99 (84-100)	102 (102-108)	109 (97-115)	90 (74-117)	96 (82-113)	106 (86-108)	106 (105-107)	102 (92-117)	94 (92-96)
Tetralogy of Fallot	137	73 (61-85)	62 (32-100)	94 (83-101)	104 (102-110)	112 (95-115)	100 (82-121)	95 (74-110)	107 (93-109)	106 (105-108)	106 (91-117)	94 (92-99)
Ebstein anomaly	40	72 (60-89)	66 (40-139)	97 (77-101)	108 (57-114)	117 (99-123)	88 (69-108)	78 (65-115)	101 (74-112)	108 (75-110)	96 (73-109)	96 (94-101)
PS/PR	50	81 (68-93)	62 (32-101)	99 (94-104)	103 (98-108)	112 (95-119)	94 (84-107)	103 (75-115)	106 (94-108)	106 (105-110)	110 (87-117)	94 (94-97)
Coartation of the aorta	70	82 (73-96)	51 (24-96)	99 (93-104)	104 (102-109)	109 (93-113)	94 (81-115)	89 (70-110)	106 (95-108)	106 (105-107)	104 (89-114)	94 (88-96)
Aortic stenosis	104	87 (74-99)	47 (23-89)	99 (92-104)	104 (102-108)	112 (109-113)	102 (80-121)	99 (79-114)	106 (100-107)	106 (105-106)	107 (89-117)	94 (94-99)
Isolated shunt	92	80 (68-91)	65 (36-116)	97 (90-104)	108 (81-114)	112 (83-119)	96 (77-116)	88 (66-106)	106 (81-109)	106 (75-110)	104 (89-115)	94 (88-99)
Other	69	77 (66-91)	51 (30-101)	96 (84-104)	104 (86-111)	113 (109-119)	94 (70-111)	96 (68-104)	106 (90-108)	106 (105-109)	109 (86-117)	94 (88-99)
total	787	74 (61-87)	61 (30-103)	96 (85-104)	104 (102-112)	112 (94-115)	94 (74-112)	95 (72-111)	106 (93-109)	106 (105-110)	105 (89-117)	94 (92-99)
Spearman correlation R to peak $\dot{V}O_2$ (p)			***-0.164*** ***(5.25×10^{-6})***	***0.391*** ***(5.49×10^{-30})***	0.034 (0.340)	0.071 (0.049)	***0.266*** ***(4.75×10^{-14})***	***0.118*** ***(9.98×10^{-4})***	0.075 (0.036)	-0.044 (0.225)	0.095 (0.008)	-0.074 (0.038)
Spearman correlation R to ADS score (p)		***-0.164*** ***(5.25×10^{-6})***		***-0.414*** ***(8.38×10^{-33})***	***-0.301*** ***(3.33×10^{-17})***	***-0.273*** ***(2.31×10^{-14})***	***-0.520*** ***(1.19×10^{-53})***	***-0.645*** ***(1.75×10^{-90})***	***-0.501*** ***(5.07×10^{-50})***	***-0.264*** ***(1.71×10^{-13})***	***-0.740*** ***(2.41×10^{-132})***	***-0.178*** ***(8.07×10^{-7})***

Table 6: Results of CPET, ADS and SF-36, presented as percentage of norm values adjusted for age and gender [median (Q1-Q3)]

5.4. Daily physical activity in adults with congenital heart disease is positively correlated with exercise capacity but not with quality of life[78]

Aim of the study

To give a broad overview of the activity patterns of adults with CHD in their daily life and to compare daily activity with objective measured exercise capacity and quality of life.

Study subjects

From October 2007 to January 2010 a total of 469 adolescent and adult patients with various congenital heart defects completed the health-related quality of life questionnaire SF-36 and performed a cardiopulmonary exercise test. Afterwards a triaxial accelerometer was given to the patients and worn over the next consecutive seven days. Cardiopulmonary exercise test in those patients was normal routine evaluation.

Due to technical problems with the device we had to drop 48 data samples. Another 43 data have to be discarded because of insufficient patients' compliance. In 191 cases a full week was recorded. In 155 cases one workday and in 32 cases one weekend day was missing. Finally, our cohort consists of 378 patients (167 female, 28.2 ± 9.1 years) with various CHD.

The study was prospectively designed and in accordance with the declaration of Helsinki (revision 2008). The study protocol was approved by the local ethical board (project number 1931/07). Some of the patients' data were already published in our previous study on depression.[80] All patients gave written informed consent.

Results

From 378 data samples, study subjects, daily physical activity variables and peak oxygen consumption were displayed in table 7.

Diagnosis	N	sex female/male	Age (years)	Moderate activity (minutes per day)	Vigorous activity (minutes per day)	Daily activity* (minutes per day)	Peak $\dot{V}O_2$ (ml/min/kg)
Cyanotic	17	7 / 10	29.4 ± 6.4	32.6 ± 35.0	3.6 ± 5.7	36.2 ± 40.5	16.2 ± 5.0
Fontan circulation	46	22 / 24	27.2 ± 7.1	49.5 ± 34.1	8.0 ± 9.8	57.5 ± 42.1	23.5 ± 8.0
TGA after atrial switch	59	22 / 37	27.7 ± 5.5	57.8 ± 35.7	8.0 ± 11.0	65.8 ± 42.4	24.8 ± 4.4
TGA no atrial switch	23	5 / 18	21.3 ± 6.6	62.6 ± 29.0	15.5 ± 20.1	78.1 ± 44.3	30.2 ± 10.4
Tetralogy of Fallot	66	31 / 35	29.3 ± 9.6	48.3 ± 31.8	5.8 ± 7.1	54.1 ± 35.7	25.6 ± 6.8
Ebstein anomaly	18	15 / 3	37.8 ± 11.7	37.4 ± 19.9	5.1 ± 7.1	42.4 ± 29.9	21.1 ± 6.4
Pulmonic Stenosis/Regurge	21	11 / 10	28.2 ± 10.9	50.1 ± 32.5	9.4 ± 11.0	59.5 ± 41.7	28.0 ± 7.6
Coarctation of the aorta	30	8 / 22	26.1 ± 8.6	57.3 ± 33.5	12.4 ± 11.1	69.7 ± 39.3	32.5 ± 9.1
Aortic stenosis	45	11 / 34	24.5 ± 8.6	56.5 ± 30.1	12.7 ± 14.6	69.2 ± 39.3	35.1 ± 7.8
Isolated shunt	36	22 / 14	32.2 ± 7.8	56.4 ± 37.2	9.0 ± 10.2	65.4 ± 42.6	27.2 ± 5.6
Other	17	11 / 6	31.8 ± 13.2	42.0 ± 17.3	7.7 ± 7.2	49.6 ± 22.2	24.5 ± 6.7
Total	378	165 / 213	28.2 ± 9.1	51.8 ± 32.7	8.8 ± 11.3	60.7 ± 39.9	26.8 ± 9.1

Table 7: Patients data according to diagnostic groups

* pooled data from moderate to vigorous activity representing all activity >3 MET.

Daily activity

Mean daily activity >3 MET was estimated to 60.7 ± 39.9 minutes per day, without any significant difference in daily activity in the diagnostic subgroups (Figure 14) after correcting the datasheet for age (ANOVA, p=0.098).

After splitting the data, 51.8 ± 32.7 minutes were of moderate and 8.8 ± 11.3 of vigorous intensity. In total 273 of the investigated patients (73.0%) meet the recommendation of daily physical activity of at least 30 minutes or more in vigorous or moderate activity in adults and at least 60 minutes in adolescents (Figure 15).

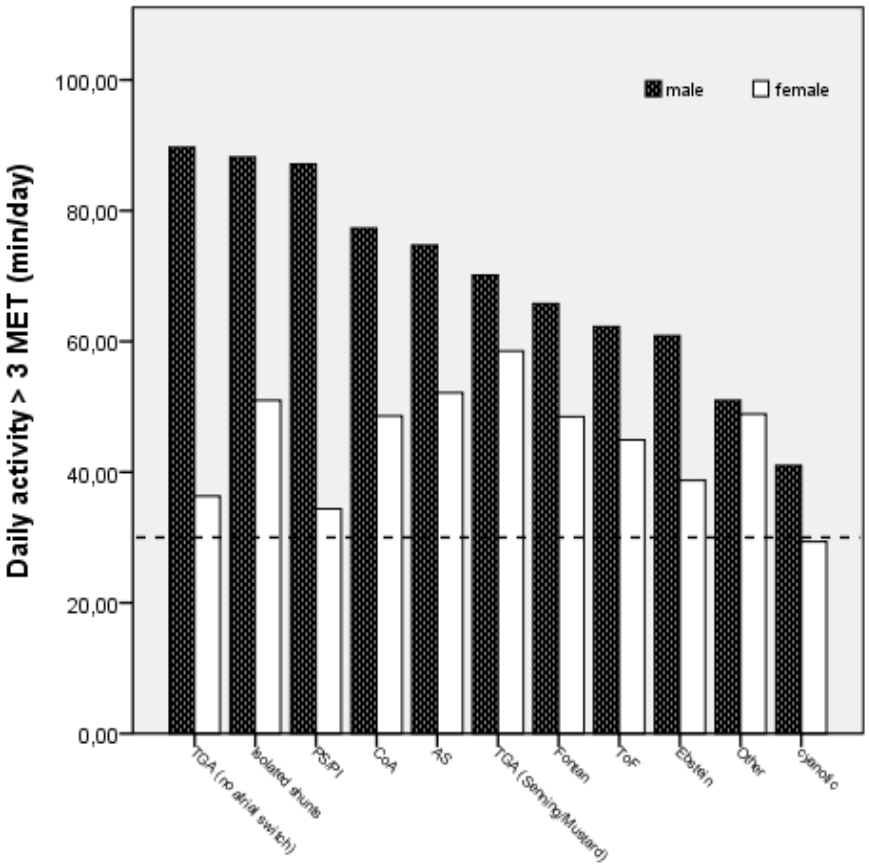

Figure 14: Mean daily activity and maximum oxygen uptake according to diagnostic subgroups. Reference line marks the recommendations for physical activity regarding to ≥ 30 minutes/day, ≥ 3 MET.

As seen in Figure 14 and Figure 15 males were significantly more active achieving 71.4 ± 44.4 minutes of activity per day in contrast to 46.8 ± 27.9 minutes achieved by females (t-test, $p=1.14x10^{-19}$). Moreover, there was a significant decrease in daily activity with increasing age (Pearson, r= -0.223, $p=1.25x10^{-5}$).

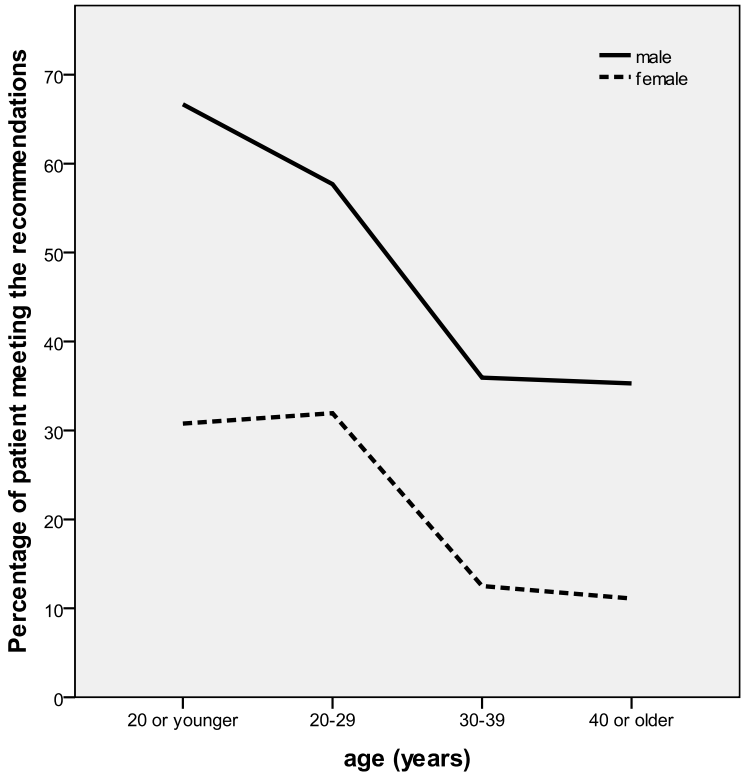

Figure 15: Percentage of patients meeting the daily activity recommendations.

Figure 16 showed that interday distribution was stable from Monday to Saturday with a slight increase over the weekdays till Friday. Only on Sundays daily activity was significantly reduced (MANOVA, p=0.023).

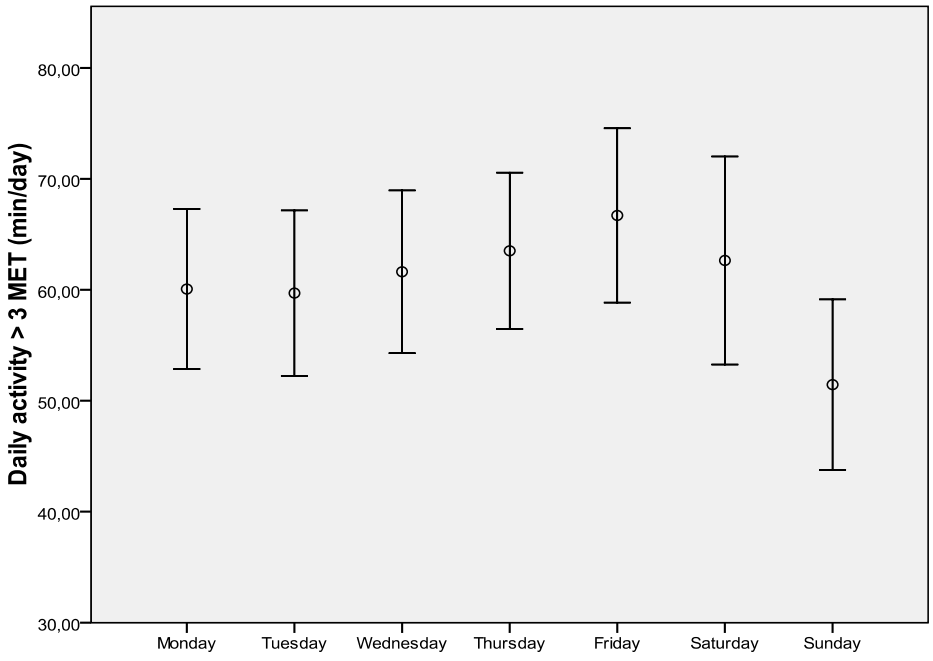

Figure 16: Daily activity according to weekdays with 95% CI (MANOVA, n=191, p=0.023)

Exercise capacity

Exercise capacity assessed as peak oxygen uptake was diminished with 26.8 ± 9.1 ml/min/kg corresponding to 74.7% ± 19.2% of the age- and sex-related reference values. Moreover, peak oxygen consumption decreased with proceeding age ($r=-0.439$, $p=3.20 \times 10^{-19}$).

There was a moderate correlation between daily activity and peak $\dot{V}O_2$ ($r=0.442$, $p=1.82 \times 10^{-19}$, Figure 17).

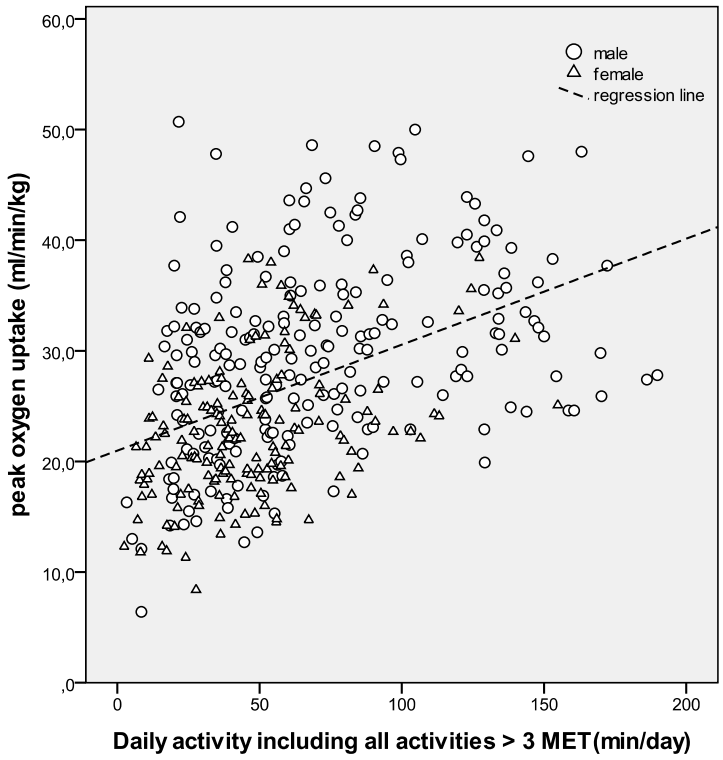

Figure 17: Coherence of daily activity and peak oxygen uptake according to sex (n=378, $r=0.442$, $p=1.82 \times 10^{-19}$)

Quality of life

Self-estimated quality of life was fairly good. In many scales, the best imaginable result was achieved in many patients. However, correlations to daily activity and exercise capacity were rather poor.

Discussion

Daily activity in congenital heart disease

Surprisingly, this study showed that 73% of our investigated patients met the recommended 30 minutes for adults and 60 minutes for adolescents of at least

moderate activity a day to maintain health and reduce the risk for cardiovascular disease. Therewith those patients were just as active as we recommend to their healthy peers.

This is in contrast to many other studies who report on alarmingly diminished physical activity. However, these studies focused only on children and adolescents with CHD.[39, 73, 106] This may indicate that these problems might not persist into adulthood. Only Dua et al. presented a small group of 61 adults with CHD with physical activity levels being between normal and severely limited.[33]

All of these recent studies outlined the need and benefit of physical activity and concluded that patients with CHD should be advised to an active lifestyle by their physician. This also changed our policy since the middle of this decade on. Patient and their parents are now advised in our institution to live an active lifestyle and to participate in leisure sports as long as clear contraindications are not present. Maybe, our patients have internalized our attitude and this paradigm shift changed their activity pattern.

This was seen already in our previous published study of younger aged Fontan patients in which 72% meet the recommendation of daily activity.[77] Nevertheless, we recognized that daily activity was diminished to healthy peers especially in the youngest patients, but this seems not to be so dramatically as primarily supposed.

Surprisingly, activity was independent of the underlying congenital heart defect after correcting the data for age. This implies that all patients with CHD, even those with severe lesions, may achieve a normal daily activity pattern as it is recommended in the guidelines.[60, 86] Nevertheless, a short look might be given to the cyanotic subgroup where activity was lowest. Some of this subgroup suffers dyspnea and fatigue already at rest making even leisure exercise nearly impossible and not advisable.

As in the healthy population,[109] gender differences in daily activity were also prominent in our cohort. As shown in the results part and figure 14 males were 53% more engaged in daily activities than females. Our data confirms the data from Fredriksen at. al[39] who has already shown the gender differences in children with CHD.

The steep decline in daily activity with age is also concordant to healthy subject.[109] It is seen in both sexes but reaching poorer values in woman older than 30 years meeting the recommendation in only 37%. This outlines that especially females are on higher risk to develop sedentary behaviors than males. Therefore, they should be screened about their daily activity and if necessary encouraged to stick to an active lifestyle and to participate in leisure sports after excluding medical hazards from cardiac residuals.

Looking on interday variability, daily activity was relatively stable from Monday to Saturday with slight increase over the week till Friday. These stable conditions are concordant to Fredriksen et al.,[39] but their patients were not as active on Saturday as our cohort. We speculate that this phenomenon is age related. Their patients were in mean aged 12.1 years, whereas our cohort was in mean 28.2 years. During weekdays everybody is participating in normal work or school activities where activity is varying not particularly. Now our cohort of adolescents and adults was more engaged in leisure and night activities on Friday and Saturday which influenced their daily activity patterns positively. Importantly, this participation also in weekend activities in patients with CHD implies a good integration to society.
However, concordant to Fredriksen et al.[39], Sunday seems to be the recovery day were activity was significant lowest due to a longer sleeping in the morning and an earlier resting in the evening.

Daily activity and exercise capacity

As frequently reported exercise capacity measured as peak $\dot{V}O_2$ was reduced in almost all patients with CHD and the degree of exercise intolerance was related to the underlying anatomical defect.[30, 80] However, we could show that exercise capacity was higher in patients with more physical activity in patients with an univentricular heart after total cavopulmonary connection.[77]
Fredriksen et al. already reported on an increased oxygen consumption after a 5 month training program twice a week.[40] Dua et al. confirmed these findings in their recent intervention study. After 10 weeks of an individual adjusted home-based walking program peak oxygen consumption increased significantly in the

61 adults with various CHD of all severities. Moreover, they showed that exercise is save and feasible in this population and simple daily activity like regular walking has already an effect on exercise capacity.[34] This is concordant to our findings that there was no difference between moderate or vigorous activity in our cohort. This implies that a dose of regular moderate activity like walking is still enough to enhance aerobic capacity in the broad majority of patients with CHD.

Daily activity and quality of life

Quality of life (QoL) was fairly good, but surprisingly there was only weak correlation between daily activity and the physical domains of QoL. This is concordant to McCrindle et al. who estimated a relation only to perceived general health in Fontan patients. Additionally, in our previous study[77] only the young children showed a significant relation to mental health. Especially for the subscale of "vitality" we assumed stronger relations to activity, but coherence was rather poor. Like often reported, there is a discrepancy between subjectively answered and objectively measured confounder of QoL in patients with CHD. Patients never experienced another situation in their life and thus adapt to their disease by coping strategies or denial mechanism.[51, 52, 77, 79, 80] Therefore we suspect that only in intervention studies like described by Dua et al.[34] and Fredriksen et al.[40] shifts in QoL could become obvious in this patient group.

Study limitation

Since our institution policy changed about this millennium and an active lifestyle is promoted by our physicians our cohort might be more active than patients with CHD being in surveillance somewhere else. The higher proportion of 56% males also might have skewed the data to a higher activity level.

6. Summary and Clinical Perspective

This thesis showed an excellent adaptation to normal life in patients with CHD. Only few need exercise restrictions because of exercise induced arrhythmia or ischemia. A great majority leads an active lifestyle, reports on good quality of life and psychological wellbeing, even though being limited in their physical performance.

Generally, the findings suggest that an active lifestyle should be promoted to most patients with CHD. Cardiopulmonary exercise testing is the key to insure the safety of activities and to depict limits in exercise capacity to caregivers and patients. Several of the older patients with CHD must be educated about active lifestyles because the restrictions given to them during childhood still exist in their mind. In addition, females particularly have a higher risk to develop sedentary behaviors and should therefore be screened with regards to their daily activity and, if necessary, be encouraged to stick to an active lifestyle and to participate in leisure sports.
Albeit being active, the great majority is limited in their exercise performance in comparison to healthy peers. Those limitations existed since childhood and almost all patients have problems in estimating their exercise performances and compare them to healthy peers. Therefore, the only way to obtain objective information for medical doctors and patients is the cardiopulmonary exercise test. If advised to stick to an active lifestyle and to participate in leisure sports, patients and doctors should be aware of the objective fitness level and possible complications during exercise and not trust the patient's self-conception.

Moreover, the findings refute the opinion that quality of life is associated with exercise performance. Patients with CHD obtain their quality of life from the more emotional and mental point of view. Participating in daily life, having friends, family and job, is much more important for them to obtain a good quality of life than physical fitness. This is the only reason why psychological condition in the vast majority of CHD was easier to measure than in healthy peers.

Parents and friends involve themselves and encourage the children to overcome their physical limitations and to communicate sorrows and fears. However, it is of great importance to detect the few who feel restricted because the impact on quality of life is tremendous.

The basic and difficult task now is how to detect patients who feel curtailed in their abilities and offer them the right treatment. This is nearly an impossible objective for the medical doctors alone and for that reason psychologists should support them in detection and offer psychological help to the patients.

In exercise and sports concerns, sports scientists should support medical doctors and patients during their outpatient visits. Screening the patients in a CPET for their exercise performance or by an accelerometer for their daily activity is a need to obtain objective information in order to advice the patients appropriately. Only from that information can an individual exercise or can sports advice be given.

Moreover, developing sports programs and supervising exercise intervention studies for clinical research is a field where a sports scientist’s help is sought.

7. Reference

1. Attenhofer Jost CH, Connolly HM, Dearani JA, Edwards WD, Danielson GK. Ebstein's anomaly. Circulation 2007;115:277-85.

2. Azakie A, McCrindle BW, Van Arsdell G, et al. Extracardiac conduit versus lateral tunnel cavopulmonary connections at a single institution: impact on outcomes. J Thorac Cardiovasc Surg 2001;122:1219-28.

3. Badiu CC, Schreiber C, Horer J, et al. Early timing of surgical intervention in patients with Ebstein's anomaly predicts superior long-term outcome. Eur J Cardiothorac Surg 2009.

4. Bertranou EG, Blackstone EH, Hazelrig JB, Turner ME, Kirklin JW. Life expectancy without surgery in tetralogy of Fallot. Am J Cardiol 1978;42:458-66.

5. Bjarnason-Wehrens B, Dordel S, Schickendantz S, et al. Motor development in children with congenital heart diseases compared to healthy peers. Eur J Cardiovasc Prev Rehabil 2006;13:S81-2.

6. Bjork VO, Olin CL, Bjarke BB, Thoren CA. Right atrial-right ventricular anastomosis for correction of tricuspid atresia. J Thorac Cardiovasc Surg 1979;77:452-8.

7. Blalock A, Hanlon CR. The surgical treatment of complete transposition of the aorta and the pulmonary artery. Surg Gynecol Obstet 1950;90:1-15, illust.

8. Blalock A, Taussig HB. The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. JAMA 1945;128:189-202.

9. Bonhoeffer P, Boudjemline Y, Saliba Z, et al. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. Lancet 2000;356:1403-5.

10. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. N Engl J Med 2000;342:256-63.

11. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. Second of two parts. N Engl J Med 2000;342:334-42.

12. Brock RC. Pulmonary valvulotomy for the relief of congenital pulmonary stenosis; report of three cases. Br Med J 1948;1:1121-6.

13. Bromberg JI, Beasley PJ, D'Angelo EJ, Landzberg M, DeMaso DR. Depression and anxiety in adults with congenital heart disease: a pilot study. Heart Lung 2003;32:105-10.

14. Brown ML, Dearani JA, Danielson GK, et al. The outcomes of operations for 539 patients with Ebstein anomaly. J Thorac Cardiovasc Surg 2008;135:1120-36, 36 e1-7.

15. Bullinger M. German translation and psychometric testing of the SF-36 Health Survey: preliminary results from the IQOLA Project. International Quality of Life Assessment. Soc Sci Med 1995;41:1359-66.

16. Bullinger M, Kirchberger I. SF-36, Fragebogen zum Gesundheitszustand, Handanweisung. 1st ed. Göttingen: Hogrefe; 1998.

17. Carabello BA, Crawford FA, Jr. Valvular heart disease. N Engl J Med 1997;337:32-41.

18. Chen CR, Cheng TO, Huang T, et al. Percutaneous balloon valvuloplasty for pulmonic stenosis in adolescents and adults. N Engl J Med 1996;335:21-5.

19. Chua TP, Ponikowski P, Harrington D, et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. J Am Coll Cardiol 1997;29:1585-90.

20. Clark AL, Poole-Wilson PA, Coats AJ. Effects of motivation of the patient on indices of exercise capacity in chronic heart failure. Br Heart J 1994;71:162-5.

21. Clark AL, Swan JW, Laney R, Connelly M, Somerville J, Coats AJ. The role of right and left ventricular function in the ventilatory response to exercise in chronic heart failure. Circulation 1994;89:2062-9.

22. Cooper CB, Storer TW. Exercise testing and interpretation; a practical approach. 1st ed: Cambridge University Press; 2001.

23. Cooper DM, Weiler-Ravell D. Gas exchange response to exercise in children. Am Rev Respir Dis 1984;129:S47-8.

24. Crafoord C, Nylin G. Congenital coarctation of the aorta and its surgical treatment. J Thorac Surg 1945;14:347-61.

25. d'Udekem Y, Iyengar AJ, Cochrane AD, et al. The Fontan procedure: contemporary techniques have improved long-term outcomes. Circulation 2007;116:I157-64.

26. Davis JA, Whipp BJ, Wasserman K. The relation of ventilation to metabolic rate during moderate exercise in man. Eur J Appl Physiol Occup Physiol 1980;44:97-108.

27. de Leval MR, Kilner P, Gewillig M, Bull C. Total cavopulmonary connection: a logical alternative to atriopulmonary connection for complex Fontan operations. Experimental studies and early clinical experience. J Thorac Cardiovasc Surg 1988;96:682-95.

28. Dilawar M, Bradley S, Saul J, Stroud M, Balaji S. Sinus node dysfunction after intraatrial lateral tunnel and extracardiac conduit fontan procedures. Pediatr Cardiol 2003;24:284-8.

29. Diller GP, Dimopoulos K, Broberg CS, et al. Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case-control study. Eur Heart J 2006;27:1737-42.

30. Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation 2005;112:828-35.

31. Dimopoulos K, Okonko DO, Diller GP, et al. Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. Circulation 2006;113:2796-802.

32. Driscoll D. Ventilatory efficiency and aerobic capacity predict event-free survival in adults with atrial repair for complete transposition of the great arteries. J Am Coll Cardiol 2009;53:1556-7.

33. Dua JS, Cooper AR, Fox KR, Graham Stuart A. Physical activity levels in adults with congenital heart disease. Eur J Cardiovasc Prev Rehabil 2007;14:287-93.

34. Dua JS, Cooper AR, Fox KR, Graham Stuart A. Exercise training in adults with congenital heart disease: feasibility and benefits. Int J Cardiol 2010;138:196-205.

35. Eisenmenger V. Die angeborenen Defekte der Kammerscheidewände des Herzens. Zeitschrift für klinische Medizin 1897;32:1-18.

36. Fallot A. Contribution à l'anatomie pathologique de la maladie bleue (cyanose cardiaque). Marseille Med 1888;25:77-93.

37. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971;26:240-8.

38. Fredriksen PM, Diseth TH, Thaulow E. Children and adolescents with congenital heart disease: assessment of behavioural and emotional problems. Eur Child Adolesc Psychiatry 2009;18:292-300.

39. Fredriksen PM, Ingjer E, Thaulow E. Physical activity in children and adolescents with congenital heart disease. Aspects of measurements with an activity monitor. Cardiol Young 2000;10:98-106.

40. Fredriksen PM, Kahrs N, Blaasvaer S, et al. Effect of physical training in children and adolescents with congenital heart disease. Cardiol Young 2000;10:107-14.

41. Fredriksen PM, Veldtman G, Hechter S, et al. Aerobic capacity in adults with various congenital heart diseases. Am J Cardiol 2001;87:310-4.

42. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet 2000;356:975-81.

43. Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. Circulation 1995;92:231-7.

44. Giannico S, Hammad F, Amodeo A, et al. Clinical outcome of 193 extracardiac Fontan patients: the first 15 years. J Am Coll Cardiol 2006;47:2065-73.

45. Giardini A, Hager A, Lammers AE, et al. Ventilatory efficiency and aerobic capacity predict event-free survival in adults with atrial repair for complete transposition of the great arteries. J Am Coll Cardiol 2009;53:1548-55.

46. Giardini A, Hager A, Napoleone CP, Picchio FM. Natural history of exercise capacity after the Fontan operation: a longitudinal study. Ann Thorac Surg 2008;85:818-21.

47. Giardini A, Hager A, Pace Napoleone C, Picchio FM. Natural history of exercise capacity after the Fontan operation: a longitudinal study. Ann Thorac Surg 2008;85:818-21.

48. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 2002;106:1883-92.

49. Glaser S, Opitz CF, Bauer U, et al. Assessment of symptoms and exercise capacity in cyanotic patients with congenital heart disease. Chest 2004;125:368-76.

50. Gratz A, Hess J, Hager A. Self estimated physical functioning does not predict actual exercise capacity in adolescents and adults with congenital heart disease. Eur Heart J 2008.

51. Gratz A, Hess J, Hager A. Self-estimated physical functioning poorly predicts actual exercise capacity in adolescents and adults with congenital heart disease. Eur Heart J 2009;30:497-504.

52. Hager A, Hess J. Comparison of health related quality of life with cardiopulmonary exercise testing in adolescents and adults with congenital heart disease. Heart 2005;91:517-20.

53. Hager A, Kaemmerer H, Eicken A, Fratz S, Hess J. Long-term survival of patients with univentricular heart not treated surgically. J Thorac Cardiovasc Surg 2002;123:1214-7.

54. Hager A, Kanz S, Kaemmerer H, Schreiber C, Hess J. Coarctation Long-term Assessment (COALA): significance of arterial hypertension in a cohort of 404 patients up to 27 years after surgical repair of isolated coarctation of the aorta, even in the absence of restenosis and prosthetic material. J Thorac Cardiovasc Surg 2007;134:738-45.

55. Hautzinger M, Bailer M. Allgemeine Depressions Skala. Manual. Göttingen: Beltz Test GmbH; 1993.

56. Hirth A, Reybrouck T, Bjarnason-Wehrens B, Lawrenz W, Hoffmann A. Recommendations for participation in competitive and leisure sports in patients with congenital heart disease: a consensus document. Eur J Cardiovasc Prev Rehabil 2006;13:293-9.

57. Jatene AD, Fontes VF, Paulista PP, et al. Successful anatomic correction of transposition of the great vessels. A preliminary report. Arq Bras Cardiol 1975;28:461-64.

58. Kamphuis M, Ottenkamp J, Vliegen HW, et al. Health related quality of life and health status in adult survivors with previously operated complex congenital heart disease. Heart 2002;87:356-62.

59. Kan JS, White RI, Jr., Mitchell SE, Gardner TJ. Percutaneous balloon valvuloplasty: a new method for treating congenital pulmonary-valve stenosis. N Engl J Med 1982;307:540-2.

60. Kavey RE, Daniels SR, Lauer RM, Atkins DL, Hayman LL, Taubert K. American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. Circulation 2003;107:1562-6.

61. Kavey RE, Thomas FD, Byrum CJ, Blackman MS, Sondheimer HM, Bove EL. Ventricular arrhythmias and biventricular dysfunction after repair of tetralogy of Fallot. J Am Coll Cardiol 1984;4:126-31.

62. Knight RG, Williams S, McGee R, Olaman S. Psychometric properties of the Centre for Epidemiologic Studies Depression Scale (CES-D) in a sample of women in middle life. Behav Res Ther 1997;35:373-80.

63. Konstantinides S, Geibel A, Olschewski M, et al. A comparison of surgical and medical therapy for atrial septal defect in adults. N Engl J Med 1995;333:469-73.

64. Kovacs AH, Saidi AS, Kuhl EA, et al. Depression and anxiety in adult congenital heart disease: Predictors and prevalence. Int J Cardiol 2008.

65. Kreutzer G, Galindez E, Bono H, De Palma C, Laura JP. An operation for the correction of tricuspid atresia. J Thorac Cardiovasc Surg 1973;66:613-21.

66. Lane DA, Lip GY, Millane TA. Quality of life in adults with congenital heart disease. Heart 2002;88:71-5.

67. Lins RF, Lins MF, Cavalcanti C, Miranda RP, Mota JH. Orthoterminal correction of congenital heart disease: double cava-pulmonary anastomosis. J Thorac Cardiovasc Surg 1982;84:633-5.

68. Longmuir PE, Turner JA, Rowe RD, Olley PM. Postoperative exercise rehabilitation benefits children with congenital heart disease. Clin Invest Med 1985;8:232-8.

69. MacLellan-Tobert SG, Driscoll DJ, Mottram CD, Mahoney DW, Wollan PC, Danielson GK. Exercise tolerance in patients with Ebstein's anomaly. J Am Coll Cardiol 1997;29:1615-22.

70. Marcelletti C, Corno A, Giannico S, Marino B. Inferior vena cava-pulmonary artery extracardiac conduit. A new form of right heart bypass. J Thorac Cardiovasc Surg 1990;100:228-32.

71. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. Circulation 2007;115:163-72.

72. Massin MM, Hovels-Gurich HH, Gerard P, Seghaye MC. Physical activity patterns of children after neonatal arterial switch operation. Ann Thorac Surg 2006;81:665-70.

73. McCrindle BW, Williams RV, Mital S, et al. Physical activity levels in children and adolescents are reduced after the Fontan procedure, independent of exercise capacity, and are associated with lower perceived general health. Arch Dis Child 2007;92:509-14.

74. Mehta PK, Simpson L, Lee EK, Lyle TA, McConnell ME, Book WM. Endothelin receptor antagonists improve exercise tolerance and oxygen saturations in patients with Eisenmenger syndrome and congenital heart defects. Tex Heart Inst J 2008;35:256-61.

75. Montis S, Atzeni C, Portas E, Congiu M, Pisanu S, Tumbarello R. The usefulness of holding in the management of congenital heart disease. Pediatr Med Chir 2008;30:244-8.

76. Moons P, Van Deyk K, De Geest S, Gewillig M, Budts W. Is the severity of congenital heart disease associated with the quality of life and perceived health of adult patients? Heart 2005;91:1193-8.

77. Müller J, Christov F, Schreiber C, Hess J, Hager A. Exercise capacity, quality of life, and daily activity in the long-term follow-up of patients with univentricular heart and total cavopulmonary connection. Eur Heart J 2009;30:2915-20.

78. Müller J, Hess J, Hager A. Daily physical activity in adults with congenital heart disease is positively correlated with exercise capacity but not with quality of life (submitted for publication).

79. Müller J, Hess J, Hager A. Exercise performance and quality of life is more impaired in Eisenmenger syndrome than in complex cyanotic congenital heart disease with pulmonary stenosis. Int J Cardiol 2010;doi:10.1016/j.ijcard.2010.04.005.

80. Müller J, Hess J, Hager A. Minor symptoms of depression in patients with congenital heart disease have a larger impact on quality of life than severely limited exercise capacity. Int J Cardiol 2010;10.1016/j.ijcard.2010.09.029.

81. Müller J, Kühn A, Vogt M, C. S, Hess J, Hager A. Improvement in exercise performance after surgery for Ebstein`s anomaly. J Thorac Cardiovasc Surg;10.1016/j.jtcvs.2010.08.083

82. Murphy JG, Gersh BJ, Mair DD, et al. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. N Engl J Med 1993;329:593-9.

83. Mustard WT. Successful Two-Stage Correction of Transposition of the Great Vessels. Surgery 1964;55:469-72.

84. Myers J, Walsh D, Buchanan N, Froelicher VF. Can maximal cardiopulmonary capacity be recognized by a plateau in oxygen uptake? Chest 1989;96:1312-6.

85. Nakano T, Kado H, Ishikawa S, et al. Midterm surgical results of total cavopulmonary connection: clinical advantages of the extracardiac conduit method. J Thorac Cardiovasc Surg 2004;127:730-7.

86. Pate RR, Freedson PS, Sallis JF, et al. Compliance with physical activity guidelines: prevalence in a population of children and youth. Ann Epidemiol 2002;12:303-8.

87. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. JAMA 1995;273:402-7.

88. Perloff JK. Congenital heart disease in adults. A new cardiovascular subspecialty. Circulation 1991;84:1881-90.

89. Popelova J, Slavik Z, Skovranek J. Are cyanosed adults with congenital cardiac malformations depressed? Cardiol Young 2001;11:379-84.

90. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Applied Psychological Measurement 1977;1:385-401.

91. Rashkind WJ, Miller WW. Creation of an atrial septal defect without thoracotomy. A palliative approach to complete transposition of the great arteries. JAMA 1966;196:991-2.

92. Reybrouck T, Mertens L. Physical performance and physical activity in grown-up congenital heart disease. Eur J Cardiovasc Prev Rehabil 2005;12:498-502.

93. Roberts RE, Vernon SW, Rhoades HM. Effects of language and ethnic status on reliability and validity of the Center for Epidemiologic Studies-Depression Scale with psychiatric patients. J Nerv Ment Dis 1989;177:581-92.

94. Rogers R, Reybrouck T, Weymans M, Dumoulin M, Van der Hauwaert L, Gewillig M. Reliability of subjective estimates of exercise capacity after total repair of tetralogy of Fallot. Acta Paediatr 1994;83:866-9.

95. Rowlands AV, Thomas PW, Eston RG, Topping R. Validation of the RT3 triaxial accelerometer for the assessment of physical activity. Med Sci Sports Exerc 2004;36:518-24.

96. Sallis JF. Epidemiology of physical activity and fitness in children and adolescents. Crit Rev Food Sci Nutr 1993;33:403-8.

97. Samanek M, Voriskova M. Congenital heart disease among 815,569 children born between 1980 and 1990 and their 15-year survival: a prospective Bohemia survival study. Pediatr Cardiol 1999;20:411-7.

98. Schreiber C, Cook A, Ho SY, Augustin N, Anderson RH. Morphologic spectrum of Ebstein's malformation: revisitation relative to surgical repair. J Thorac Cardiovasc Surg 1999;117:148-55.

99. Schulze-Neick I, Gilbert N, Ewert R, et al. Adult patients with congenital heart disease and pulmonary arterial hypertension: first open prospective multicenter study of bosentan therapy. Am Heart J 2005;150:716.

100. Senning A. Surgical correction of transposition of the great vessels. Surgery 1959;45:966-80.

101. Somerville J. Grown-up congenital heart (GUCH) disease: current needs and provision of service for adolescents and adults with congenital heart disease in the UK. Heart 2002;88 Suppl 1:i1-14.

102. Spijkerboer AW, Utens EM, Bogers AJ, Verhulst FC, Helbing WA. Long-term behavioural and emotional problems in four cardiac diagnostic groups of children and adolescents after invasive treatment for congenital heart disease. Int J Cardiol 2008;125:66-73.

103. Stefan MA, Hopman WM, Smythe JF. Effect of activity restriction owing to heart disease on obesity. Arch Pediatr Adolesc Med 2005;159:477-81.

104. Sullivan MJ, Higginbotham MB, Cobb FR. Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. Circulation 1988;77:552-9.

105. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Gas exchange detection of exercise-induced right-to-left shunt in patients with primary pulmonary hypertension. Circulation 2002;105:54-60.

106. Swan L, Hillis WS. Exercise prescription in adults with congenital heart disease: a long way to go. Heart 2000;83:685-7.

107. Ternestedt BM, Wall K, Oddsson H, Riesenfeld T, Groth I, Schollin J. Quality of life 20 and 30 years after surgery in patients operated on for tetralogy of Fallot and for atrial septal defect. Pediatr Cardiol 2001;22:128-32.

108. Thaulow E, Fredriksen PM. Exercise and training in adults with congenital heart disease. Int J Cardiol 2004;97 Suppl 1:35-8.

109. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008;40:181-8.

110. Trojnarska O, Gwizdala A, Katarzynski S, et al. The BNP concentrations and exercise capacity assessment with cardiopulmonary stress test in cyanotic adult patients with congenital heart diseases. Int J Cardiol 2008.

111. Trojnarska O, Gwizdala A, Katarzynski S, et al. Evaluation of exercise capacity with cardiopulmonary exercise test and B-type natriuretic peptide in adults with congenital heart disease. Cardiol J 2009;16:133-41.

112. Utens EM, Verhulst FC, Erdman RA, et al. Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: a follow-up study. J Psychosom Res 1994;38:745-58.

113. Utens EM, Verhulst FC, Meijboom FJ, et al. Behavioural and emotional problems in children and adolescents with congenital heart disease. Psychol Med 1993;23:415-24.

114. van Rijen EH, Utens EM, Roos-Hesselink JW, et al. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. Eur Heart J 2003;24:673-83.

115. Vigl M, Hager A, Bauer U, et al. Sexuality and subjective wellbeing in male patients with congenital heart disease. Heart 2009;95:1179-83.

116. Warnes CA. The adult with congenital heart disease: born to be bad? J Am Coll Cardiol 2005;46:1-8.

117. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Circulation 2008;118:e714-833.

118. Washington RL, Bricker JT, Alpert BS, et al. Guidelines for exercise testing in the pediatric age group. From the Committee on Atherosclerosis and Hypertension in Children, Council on Cardiovascular Disease in the Young, the American Heart Association. Circulation 1994;90:2166-79.

119. Wasserman K, Whipp BJ, Koyl SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. J Appl Physiol 1973;35:236-43.

120. Waurick PE, Kleber FX. Cardiopulmonary Exercise Testing in Pulmonary Vascular Disease: Arterial and End-Tidal CO_2 Partial Pressures in Patients with Acute and Chronic Pulmonary Embolism and Primary Pulmonary Hypertension. In: Wasserman K, ed. Cardiopulmonary Exercise Testing and Cardiovascular Health. Armonk, NY: Futura Publishing Company, Inc; 2002:173-8.

121. Whipp BJ, Ward SA. Determinants and control of breathing during muscular exercise. Br J Sports Med 1998;32:199-211.

122. Wood P. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. Br Med J 1958;2:755-62.

8. Appendix

Questionnaires used in the study:

Medical Outcomes Study 36 Item Short Form (SF-36)

Allgemeine Depressionsskala (ADS)

Publications:

Müller J, Christov F, Schreiber C, Hess J, Hager A. Exercise capacity, quality of life, and daily activity in the long-term follow-up of patients with univentricular heart and total cavopulmonary connection. *Eur Heart J* 2009; 30(23):2915-2920.

Müller J, Hess J, Hager A. Exercise performance and quality of life is more impaired in Eisenmenger syndrome than in complex cyanotic congenital heart disease with pulmonary stenosis. *Int J Cardiol*; doi:10.1016/j.ijcard. 2010.04.005.

Müller J, Hess J, Hager A. Minor symptoms of depression in patients with congenital heart disease have a larger impact on quality of life than limited exercise capacity. *Int J Cardiol.* doi:10.1016/j.ijcard.2010.09.029.