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# Effects of Congenital Heart Disease Treatment on Quality of Life:
## A Longitudinal Study of Adolescents and Adults

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# Abstract

Due to the rising survival rate of patients with congenital heart disease (CHD), functional health variables such as health-related quality of life (HRQoL) and objectively measured exercise capacity have become key aspects for the evaluation of health-care outcomes. The effectiveness of the various treatment options in terms of functional health in adolescents and adults with CHD remains largely unclear. In this retrospective, longitudinal study, we found that generally active treatment was associated with better HRQoL over time. Adolescent and adult patients reported better physical HRQoL after surgery and catheter intervention, despite this effect not being apparent in the objectively measured exercise capacity. Changes in HRQoL did not correlate with changes in exercise capacity over time. Hence, parallel assessment of HRQoL and exercise capacity is essential in the evaluation of adolescents and adults with CHD.



# Zusammenfassung

Aufgrund der steigenden Überlebensrate von Patienten mit angeborenen Herzfehlern (AHF) sind funktionale Gesundheitsvariablen wie die gesundheitsbezogene Lebensqualität und die Leistungsfähigkeit essenziell für die Evaluation dieser Patienten geworden. Die Effektivität der unterschiedlichen Therapieoptionen bezüglich Veränderungen von funktionalen Gesundheitsvariablen in Jugendlichen und Erwachsenen mit AHF ist noch unklar. In dieser retrospektiven, longitudinalen Studie beobachteten wir, dass im Allgemeinen eine aktive Therapie mit besserer gesundheitsbezogener Lebensqualität verbunden war. Jugendliche und Erwachsene mit AHF gaben eine bessere physische Lebensqualität nach einer Operation und Herzkatheterintervention an, obwohl dieser Effekt nicht in einer Verbesserung der objektiven Leistungsfähigkeit nachweisbar war. Veränderungen in der gesundheitsbezogenen Lebensqualität korrelierten nicht mit Veränderungen in der Leistungsfähigkeit. Daher ist die parallele Erfassung von gesundheitsbezogener Lebensqualität und Leistungsfähigkeit für die Evaluation von Jugendlichen und Erwachsenen mit AHF erforderlich.

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| | |
|---|---|
| ACHD | Adults with congenital heart disease |
| ASD | Atrial septal defect |
| AVSD | Atrioventricular septal defect |
| BP | Blood pressure |
| ccTGA | Congenitally corrected transposition of the great arteries |
| CHD | Congenital heart disease |
| CO | Cardiac output |
| CoA | Coarctation of the aorta |
| CPET | Cardiopulmonary exercise testing |
| CT | Computed tomography |
| DORV | Double outlet right ventricle |
| Ebstein | Ebstein's anomaly |
| ECG | Electrocardiography |
| HCM | Hypertrophic cardiomyopathy |
| HFpEF | Heart failure with preserved ejection fraction |
| HR | Heart rate |
| HRQoL | Health-related quality of life |
| ICD | Implantable cardioverter-defibrillator |
| LRS | Left-to-right shunt |
| MAP | Mean arterial pressure |
| MRI | Magnetic resonance imaging |
| PAPVR | Partial anomalous pulmonary venous return |
| PA/VSD | Pulmonary atresia and ventricular septal defect |
| $PETO_2$ | End-tidal pressure for $O_2$ |
| $PETCO_2$ | End-tidal pressure for $CO_2$ |
| PDA | Patent ductus arteriosus |
| PFO | Patent foramen ovale |
| PRO | Patient-reported outcome |
| QoL | Quality of life |
| RER | Respiratory exchange ratio |
| RLS | Right-to-left shunt |
| RR | Respiratory rate |
| SV | Stroke volume |
| TAC | Truncus arteriosus communis (common arterial trunk) |
| TAPVR | Total anomalous pulmonary venous return |
| TGA | Transposition of the great arteries |
| TOF | Tetralogy of Fallot |
| UVH | Univentricular heart/ single ventricle |

| | |
|---|---|
| vAS | Valvular aortic stenosis |
| $\dot{V}CO_2$ | Carbon dioxide output |
| $\dot{V}E$ | Respiratory minute ventilation |
| $\dot{V}O_2$ | Oxygen uptake |
| VSD | Ventricular septal defect |
| vPS | Valvular pulmonary stenosis |
| VT | Ventilatory threshold |
| Vt | Tidal volume |
| WR | Work rate |

# 1 Introduction

Remarkable diagnostic and therapeutic advancements have been accomplished in the field of congenital heart disease (CHD) in the last decades. Especially, improvements in cardiac surgery, intensive care as well as catheter interventions have led to a significant decrease in infant mortality, with the majority of patients with CHD reaching adolescence and adulthood (Khairy et al., 2010).The number of grown-ups with CHD is continuously rising, with the latest estimates indicating that adult patients have outnumbered children (Marelli et al., 2014; Webb, 2001).

Therefore, the key measure for the evaluation of health-care outcomes in adolescents and adults with CHD is not only mortality anymore, but also other variables associated with functional health. These include objective measures like echocardiography, cardiovascular magnetic resonance imaging (MRI) and exercise capacity as well as patient-reported outcomes like health-related quality of life (HRQoL). Being a measure of health and well-being from the patients' point of view, HRQoL is particularly relevant for patients with chronic disease facing lifelong impairments. In the field of CHD, HRQoL is used not only in the health monitoring of individual patients but also in large-scale clinical studies aiming at better understanding the characteristics of this patient group and the factors influencing their well-being (Fteropoulli, Stygall, Cullen, Deanfield, & Newman, 2013; Kahr, Radke, Orwat, Baumgartner, & Diller, 2015; Luyckx, Missotten, Goossens, & Moons, 2012; Muller, Berner, Ewert, & Hager, 2014a; Opic et al., 2016; Schoormans et al., 2014). The relationship between subjective HRQoL and objective measurements like exercise capacity has also been extensively studied in this patient population (Amedro et al., 2016b; Ehlert, Hess, & Hager, 2012; Gratz, Hess, & Hager, 2009).

The therapeutic possibilities available for adolescents and adults with CHD are constantly expanding as new drugs as well as surgical and interventional devices and techniques are being developed. In order to provide our patients with optimal care, the effectiveness of the various treatment options needs to be thoroughly evaluated and compared, with functional variables such as HRQoL and exercise capacity serving as the main endpoints. To date, research has not yet adequately addressed this need. With a few exceptions (Mohr et al., 2014; Muller et al., 2014b; Penha et al., 2015), existing studies in patients with CHD are mostly cross-sectional, thus not allowing us to draw solid conclusions regarding the actual effects of the different therapeutic options. Moreover, the majority of treatment studies focus on children with CHD. However, children differ significantly from their adult counterparts with regard to

cardiac defect pathophysiology, co-morbidities as well as cognitive and emotional functioning. Lastly, existing studies usually investigate a single treatment method, mostly a specific surgical or interventional procedure (Bertoletti, Marx, Hattge, & Pellanda, 2015; Heusch, Calaminus, Kahl, & Schmidt, 2014; Latal, Helfricht, Fischer, Bauersfeld, & Landolt, 2009; Loup et al., 2009; Muller, Christov, Schreiber, Hess, & Hager, 2009; Muller et al., 2014b; Muller et al., 2011b).

Taken together, the effectiveness of the various treatment options in terms of changes in functional health over time remains unclear in adolescents and adults with CHD; hence, its investigation was the primary aim of this study.

An overview of the theoretical background of this study is presented in the following subsections (1.1 -1.4).

## 1.1 Congenital heart disease (CHD)

### 1.1.1 Epidemiology

CHD is the most common congenital anomaly in newborns, accounting for almost one-third of all major congenital anomalies. Its incidence is estimated to be approximately 8 per 1,000 live births with significant regional variations. The highest birth prevalence has been reported in Asia with 9.3 per 1,000 live births, while North America shows markedly lower numbers with 6.9 per 1,000 live births. In Europe, CHD birth prevalence lies somewhere in between, with 8.2 per 1,000 live births. (van der Linde et al., 2011) More than 6,000 babies with CHD are born every year in Germany (Kaemmerer & Hess, 2005; Schwedler et al., 2011).

In general, preterm babies present almost twice as many cardiovascular malformations compared to babies born at term (Tanner, Sabrine, & Wren, 2005). Most of the congenital cardiovascular malformations (ca. 60%) are simple, while the rest is more complex (Schwedler et al., 2011). In approximately one out of four cases, CHD is associated with further extra-cardiac anomalies, most commonly affecting the urinary tract as well as the musculoskeletal, digestive, and central nervous systems. The presence of congenital extra-cardiac anomalies may substantially influence the clinical presentation of the patient and affects morbidity and mortality independently from the cardiac defect (Stoll, Dott, Alembik, & Roth, 2015).

### 1.1.2 Etiology

Congenital cardiovascular defects arise in the early weeks of pregnancy due to disorders in the embryonic development of the heart and the surrounding vessels. The etiology is mostly multifactorial and is influenced by various genetic and environmental factors.

Nevertheless, specific genetic anomalies and environmental factors are known to be directly associated with the presence of distinct congenital cardiovascular malformations. Some characteristic examples are the following (Schumacher, Hess, & Bühlmeyer, 2008; Zipes, Libby, Bonow, Mann, & Tomaselli, 2018):

- Chromosomal aberrations:
    - Down-syndrome (47XX/XY +21) - atrioventricular canal defects
    - Turner-syndrome (45X0) - bicuspid aortic valves, coarctation of the aorta (CoA)

- Microdeletion syndromes:
    - Di-George syndrome (del22q11.2) - conotruncal anomalies, tetralogy of Fallot (TOF)
    - Williams-Beuren-Syndrome (del7q11.23) - supravalvular aortic stenosis
- Isolated gene mutations with mendelian inheritance:
    - Noonan-syndrome (autosomal dominant) - pulmonary valve stenosis
    - Marfan-syndrome (autosomal dominant) - aortic root dilation
- Environmental factors:
    - Primary rubella infection during pregnancy – patent ductus arteriosus (PDA), septal defects
    - Maternal lithium use during pregnancy - tricuspid valve anomalies

(Schumacher et al., 2008; Zipes et al., 2018)

Offspring of patients with CHD is at only slightly elevated risk of having CHD compared to the general population. In general, the average recurrence rate of CHD when one parent is affected ranges from 2 to 4%, with higher rates for specific defects such as aortic stenosis and ventricular septum defect (VSD). Interestingly, the recurrence rate is higher when the mother -rather than father- is affected. Nevertheless, in cases of isolated gene mutations or chromosomal aberrations, such as Marfan or Di-George syndrome, the recurrence rate can be as high as 50%. (Baumgartner et al., 2010; Nora & Nora, 1987)

### 1.1.3 Forms of CHD

The anatomic normal heart consists of four chambers: the right and left atrium as well as the right and left ventricle. Physiologically, the right atrium is connected to the right ventricle (right heart) and the left atrium to the left ventricle (left heart), forming the so-called concordant atrioventricular connection. The connection of each atrium to the associated ventricle is established by the atrioventricular valves: the mitral valve (bicuspid valve) in the left heart and the tricuspid valve in the right heart. Each ventricle is connected to one of the great arteries by a semilunar valve: the morphologic right ventricle is connected to the pulmonary artery by the pulmonary valve, while the morphologic left ventricle is connected to the aorta by the aortic valve (concordant ventriculoarterial connection).

Blood with low oxygen content from the systemic circulation drains to the right atrium and consequently to the right ventricle, which pumps it through the pulmonary artery to the pulmonary circulation. In the lungs, the blood is enriched with oxygen and oxy-

genated blood drains through the four main pulmonary veins to the left atrium and consequently to the left ventricle. The left ventricle pumps oxygenated blood through the aorta to the systemic circulation, which supplies all organs with oxygenated blood.

Congenital heart defects arise when any part of the physiologic cardiovascular development is disturbed. They may present isolated or combined. Developmental disorders may affect various processes, including vascular and cardiac valve formation, atrioventricular and ventriculoarterial connection, or the septation of the heart chambers.

According to the **clinical presentation**, CHD can be characterized as primary acyanotic or primary cyanotic (Engelfriet et al., 2005; Schumacher et al., 2008; Schwedler et al., 2011; Zipes et al., 2018):

- Acyanotic lesions (more common): They mainly include obstructive defects with no shunt (e.g. aortic valve stenosis) as well as defects with left-to-right shunt (e.g. atrial septal defect). Uncorrected left-to-right shunt defects can lead to the development of pulmonary hypertension due to high pulmonary flow and consequently to Eisenmenger syndrome with secondary cyanosis.

- Cyanotic lesions (less common): They may be associated with low pulmonary flow (e.g. tetralogy of Fallot) or high pulmonary flow with high risk for pulmonary hypertension (e.g. transposition of the great arteries, common arterial trunk). They also include lesions with a single functional ventricle (e.g. hypoplastic left heart syndrome). They are associated with higher all-cause mortality and highest rates of cardiovascular death.

(Engelfriet et al., 2005; Schumacher et al., 2008; Schwedler et al., 2011; Zipes et al., 2018)

According to **hemodynamic criteria**, CHD can be classified into four groups (Schumacher et al., 2008):

- septal defects and vascular connection disorders leading to a primary left-to-right shunt (LRS),
- right-side obstruction,
- left-side obstruction, and
- anomalies of the origin of the great arteries.

Tables 1-4 present an overview of the most common defects of each category with their associated frequency in infancy in descending order according to the Prevalence

of CHD in infants (PAN)-study of the German competence network for CHD (Schwedler et al., 2011). Very rare defects (prevalence <0.4%) are not included in this overview. Of note, the exact prevalence of CHD varies in literature and register studies. The results of the PAN study show similar results to other European studies, especially regarding severe defects.

As shown in tables 1-4, the most frequent lesions in infancy overall are ventricular septal defects (VSD), accounting for almost half of all CHD, followed by atrial septal defects (ASD) and pulmonary valve stenosis (vPS). With regard to severe lesions, the most frequent CHD is univentricular heart (UVH) followed by tetralogy of Fallot (TOF) and transposition of the great arteries (TGA). (Schwedler et al., 2011)

**Table 1: Most common septal defects and vascular connection disorders with left-right-shunt**

| CHD | Fre-quency* | Description** |
|---|---|---|
| VSD | 48.9% | **Most common CHD**. Four types according to location: perimembranous (most common), conoventricular, inlet, and muscular. Leads to direct connection between left and right ventricle with initial LRS. Small defects often remain asymptomatic and may close spontaneously. Larger defects cause heart failure symptoms and pulmonary hypertension within the first months of life. In these cases, surgical or interventional closure is indicated early during infancy. Postoperative complications include arrhythmias, sometimes requiring pacemaker implantation. |
| ASD | 17.0% | **Second most common CHD**. Two types according to location: ostium secundum-Type II (most common) and ostium primum-Type I. Leads to direct connection between left and right atrium with initial LRS. Smaller defects often remain asymptomatic until adulthood. Typical symptoms of uncorrected ASD include supraventricular arrhythmias, paradoxical embolism, heart failure symptoms and pulmonary hypertension sometimes leading to secondary cyanosis. Treatment of hemodynamic relevant ASD consists of interventional (usually method of choice) or surgical closure during early childhood or after detection. |
| PDA | 4.3% | Persistence of the fetal connection between aorta and pulmonary artery with LRS. Complications include decreased perfusion of internal organs and lower extremities, heart failure and pulmonary hypertension. Treatment: prostaglandin-synthesis inhibitors such as Indomethacin especially in preterm infants; interventional (coil or occluder) or surgical closure. |
| AVSD | 2.5% | Disturbed fusion of the endocardial cushions with the atrial septum and the muscular portion of the ventricular septum creating variable connections between the four chambers. Uncorrected, it leads to heart failure and pulmonary hypertension with secondary cyanosis. Treatment of choice is surgical repair, usually during infancy. |
| TAPVR | 0.6% | All four pulmonary veins are abnormally connected to the systemic circulation and do not drain into the left atrium. Survival after birth requires the presence of a shunt (eg. PDA or ASD). In case of additional obstruction (at the connection site of a pulmonary vein with the draining vessel), it may cause pulmonary hypertension and secondary cyanosis. Treatment of choice is surgical repair. |
| TAC | 0.5% | One common arterial trunk drains both ventricles and supplies the pulmonary and systemic circulation (including the coronary arteries) with mixed blood. It leads to pulmonary hypertension and heart failure. Treatment consists of surgical repair with conduit in the newborn period. Further surgical procedures may be required after initial repair. |
| PAPVR | 0.4% | Some (but not all) pulmonary veins are abnormally connected; usually markedly milder than TAPVR or even similar to an ASD. |

**According to the Prevalence of CHD in infants (PAN)-study of the German competence network for CHD (Schwedler et al., 2011)*

***(Schumacher et al., 2008; Zipes et al., 2018)*

*ASD* *Atrial septal defect*
*AVSD* *Atrioventricular septal defect*
*LRS* *Left-to-right shunt*
*PAPVR* *Partial anomalous pulmonary venous return*
*PDA* *Patent ductus arteriosus*
*TAC* *Truncus arteriosus communis (common arterial trunk)*
*TAPVR* *Total anomalous pulmonary venous return*
*VSD* *Ventricular septal defect*

## Table 2: Most common CHD with right-side obstruction

| CHD | Frequency* | Description** |
|---|---|---|
| vPS | 6.1% | **Third most common CHD**. Leads to increased right ventricular pressure with subsequent right ventricular hypertrophy and ultimately heart failure. Cyanosis and arrhythmias may also occur. The time of treatment depends on the severity of the condition; mild cases often do not require treatment and remain stable through childhood and adulthood, while severe cases may require emergency postnatal interventions. The treatment of choice is usually interventional balloon valvuloplasty. Alternatively, surgical repair or valve replacement may be performed. |
| TOF | 2.5% | Right and anterior deviation of the ventricular outlet septum resulting in pulmonary stenosis (with reduced pulmonary flow), malalignment VSD, overriding aorta and right ventricular hypertrophy. The hemodynamic relevance of the condition depends mainly on the grade of the right-side obstruction; mild obstruction is associated with LRS and occasional hypoxia episodes with cyanosis, while severe obstruction is associated with RLS and severe cyanosis. Untreated TOF leads to heart failure. TOF is typically treated with surgical repair during infancy. |
| PA/VSD | 0.6% | A severe form of TOF. Survival requires the presence of shunts such as a PDA or collaterals. The treatment initially consists of a palliative arterial shunt between the aorta and the pulmonary artery. Later, surgical correction is performed, often using a valved conduit. |
| Ebstein | 0.4% | The septal and posterior tricuspid valve leaflets are displaced towards the apex of the right ventricle leading to an “atrialization” of the right ventricle with enlargement of the right atrium; it is often associated with a PFO or ASD and arrhythmias. Leads to reflux of blood from the right ventricle to the right atrium and to RLS with cyanosis through the PFO/ASD combined with reduced pulmonary flow. In severe cases, the treatment of choice consists of surgical repair with primary goal to preserve the native tricuspid valve. |

**According to the Prevalence of CHD in infants (PAN)-study of the German competence network for CHD (Schwedler et al., 2011)*
***(Schumacher et al., 2008; Zipes et al., 2018)*

| | | | |
|---|---|---|---|
| *Ebstein* | *Ebstein’s anomaly* | *RLS* | *Right-to-left shunt* |
| *LRS* | *Left-to-right shunt* | *TOF* | *Tetralogy of Fallot* |
| *PA/VSD* | *Pulmonary atresia and ventricular septal defect* | *vPS* | *Valvular pulmonary stenosis* |

## Table 3: Most common CHD with left-side obstruction

| CHD | Frequency* | Description** |
|---|---|---|
| CoA | 3.6% | Narrowing of the aorta at the insertion site of the ductus arteriosus (later ligamentum arteriosum). The complete form is the interrupted aortic arch (birth prevalence 0.3%). Severity and manifestation depend on the severity of the narrowing. The survival of the infant can be dependent on a PDA; symptoms of less prominent coarctations are hypertension in the upper body and formation of collaterals (often asymptomatic until adulthood). Treatment of choice is surgical repair with resection of the coarctation and re-anastomosis. |
| vAS | 2.2% | Often associated with a bicuspid aortic valve. Leads to increased left ventricular pressure with subsequent left ventricular hypertrophy and heart failure in severe cases (usually in infancy). The time of treatment depends on the severity of the condition; mild cases often do not require treatment. For more severe cases, the treatment of choice is interventional balloon valvuloplasty during childhood. Alternatively, surgical repair or valve replacement may be performed. A surgical procedure often performed in young children is the Ross operation: the patient's pulmonary valve is transplanted to the aortic valve position and the pulmonary valve is replaced with a homograft. |

**According to the Prevalence of CHD in infants (PAN)-study of the German competence network for CHD (Schwedler et al., 2011)*
***(Schumacher et al., 2008; Zipes et al., 2018)*

| | | | |
|---|---|---|---|
| *CoA* | *Coarctation of the aorta* | *vAS* | *Valvular aortic stenosis* |

## Table 4: Most common anomalies of the origin of the great arteries

| CHD | Frequency* | Description** |
|---|---|---|
| UVH | 2.8% | A group of defects with absence of two developed ventricles with inlet and outlet parts; usually, both atria are related to one functional ventricle. It includes double inlet left ventricle, tricuspid atresia, and the hypoplastic left heart syndrome. In a UVH, the single functional ventricle pumps mixed blood both to the pulmonary and the systemic circulation. The clinical manifestation depends on the specific characteristics of each condition, consisting mainly of cyanosis and heart failure symptoms. Survival usually depends on existing shunts. The treatment consists of surgical repair in three stages: it usually starts in the newborn period with a palliative procedure such as a Blalock-Taussig shunt (to increase pulmonary flow) or a pulmonary artery banding (to reduce pulmonary flow, followed by a partial cavopulmonal connection eg. Glenn-procedure, and finally the completion of the Fontan procedure with a total cavopulmonary connection. This final step leads to the complete separation of the pulmonary and the systemic circulation with resolution of cyanosis. The deoxygenated blood from the periphery drains passively into the lungs, becomes oxygenated and is then pumped by the single ventricle to the periphery. |
| TGA | 2.2% | Ventriculoarterial discordance with the aorta arising from the right ventricle and the pulmonary artery from the left ventricle, leading to cyanosis. Survival after birth depends on the persistence of shunts (PFO, PDA) that allow some mixing of deoxygenated with oxygenated blood. The treatment usually consists of a primary palliative procedure such as the Rashkind balloon atrial septostomy, followed by a correction in form an arterial switch operation. Alternatively, a Senning or Mustard atrial switch operation or a Rastelli procedure with conduits may be performed. |
| DORV | 1.0% | Both great arteries connect totally or partially to the right ventricle with a VSD present; it may be associated with a PS or a TGA. The hemodynamic situation depends on the specific anatomic morphology. The treatment of choice is surgery. The surgical procedure performed depends on the specific defect and aims at the correction of the defect with the creation of an as normal as possible morphologic situation. In rare cases, a Fontan procedure may be necessary. |
| ccTGA | 0.3% | Ventriculoarterial discordance combined with atrioventricular discordance, i.e. ventricular inversion. This lesion is acyanotic. Often associated with further defects such as ASD, VSD, PFO and PDA. Simple cases may remain asymptomatic and require no treatment. In a number of cases, a double arterial switch operation has been performed in recent years. |

** According to the Prevalence of CHD in infants (PAN)-study of the German competence network for CHD (Schwedler et al., 2011)*

***(Schumacher et al., 2008; Zipes et al., 2018)*

*ccTGA* *Congenitally corrected transposition of the great arteries*
*DORV* *Double outlet right ventricle*
*TGA* *Transposition of the great arteries*
*UVH* *Univentricular heart/ single ventricle*

### 1.1.4 Management of patients with CHD

The primary diagnosis of CHD can take place at any time from the prenatal phase to adulthood depending on the type and severity of the defect. Survivors with native or corrected CHD often face lifelong cardiovascular complications, which can vary greatly between patients and depend mainly on the type of the defect and the age of the patient. Major cardiovascular complications include congestive heart failure, cyanosis leading to hypoxia, secondary erythrocytosis and hyperviscosity syndrome, pulmonary hypertension, Eisenmenger syndrome leading to secondary cyanosis, infective endocarditis, as well as cardiac arrhythmias and even sudden cardiac death. (Engelfriet et al., 2005; Zipes et al., 2018) Arrhythmias are mostly associated with previous operated CHD and often have supraventricular rather than ventricular origin (Engelfriet et al., 2005).

There is a wide range of available **diagnostic tools** used for the detection of the initial cardiovascular defect and its complications. Traditionally, medical history, physical examination and electrocardiography (ECG) play a central role in the diagnostic procedure. Echocardiography (transthoracic or transesophangeal) also belongs to the standard examinations conducted to evaluate cardiovascular morphology as well as function. Further diagnostic tools include non-invasive cardiovascular MRI, chest X-ray, computed tomography (CT), as well as the invasive cardiac catheterization. In cases of suspected arrhythmias, long-term ECG monitoring or event recorders are often used. Finally, especially in long-term follow up functional testing such as pulmonary function testing, the 6-min-walk test, and cardiopulmonary exercise testing are regularly performed. (Schumacher et al., 2008; Zipes et al., 2018)

The **therapeutic possibilities** available for patients with CHD are variable and range from simple surveillance to complex cardiac surgery. In general, there are four main types of treatment:

- surgery,
- catheter intervention,
- medication (drug treatment), and
- surveillance (monitoring with no change in treatment).

The aims of therapy may include correction/repair of the defect, palliation, or management of residual conditions (usually lifelong).

Correction/ repair:

Per definition, the term correction refers to the creation of a morphologically and functionally normal heart with no complications needing further surgery or interventions and a normalization of the life span. Since this is only feasible in very few cases, such as a small ASD closure, the term correction is usually used in a wider sense, typically referring to all procedures that aim to establish sequential blood flow (lung via heart to peripheral circulation and back) without shunt or stenosis. The terms correction and repair are often used interchangeably. (Joffs & Sade, 2000; Kaemmerer & Hess, 2005; Stark, 1989)

**Anatomic correction** typically refers to procedures that aim to create normal cardiac anatomy, like the operative ASD or VSD closure or the arterial switch-operation for TGA. Catheter intervention has greatly evolved over the last decades and is increasingly used as an alternative to surgery. Several interventional procedures can be offered as definitive therapeutic options, such as interventional ASD or PDA closure, pulmonary valvuloplasty or valve replacement, as well as balloon angioplasty and stenting of CoA. (Schumacher et al., 2008)

In other cases, the procedure aims "only" at a **hemodynamic correction** of the cardiac lesion without the creation of normal anatomy. These surgical procedures aiming at functional correction are often described as definitive palliative procedures and they include the Senning or Mustard atrial switch procedures for TGA, tricuspid valve reconstruction or replacement in Ebstein's anomaly, as well as the Fontan-procedure for patients with UVH. (Schumacher et al., 2008)

Usually, surgical or interventional correction is performed during infancy or childhood, especially in cases of more complex lesions. However, corrective procedures may also be performed later in adult life, either because the defect was not detected earlier or because it was not considered severe enough to undergo surgery in childhood. For instance, ASD closure is amongst the procedures commonly performed in adults with CHD (Engelfriet et al., 2005).

Palliation:

In cases where primary anatomic or functional correction is not possible, palliative procedures may be performed to prolong survival, alleviate symptoms or prepare the patient for a later correction surgery. Examples of surgical palliative procedures are the arteriopulmonary Blalock-Taussig-shunt in patients with pulmonary atresia or the cavopulmonary shunt in complex cyanotic heart disease. Catheter interventions like

the Rashkind balloon atrial septostomy are also used in the context of palliation. (Joffs & Sade, 2000; Schumacher et al., 2008)

Lifelong treatment of residuals:

In most cases, even after primary surgical or interventional repair of CHD, lifelong residuals, such as scaring or the presence of substitute material, remain. These residuals usually require lifelong monitoring and management. More specifically, many adult patients require some form of chronic medication such as beta-blockers, angiotensin converting enzyme (ACE)-inhibitors, antiarrhythmic drugs or antithrombotic agents, especially in more severe CHD (Engelfriet et al., 2005; Opic et al., 2015). Furthermore, residual conditions may also require further interventional or surgical procedures during adulthood (Berdat, Immer, Pfammatter, & Carrel, 2004). Common procedures performed in previously operated adolescents and adults with CHD include elimination of vessel or valve stenosis, valve reconstruction or replacement as well as conduit replacement. In the presence of cardiac arrhythmias, which are relatively common in previously operated patients, interventional ablation, antiarrhythmic surgery or the implantation of a pacer or implantable cardioverter-defibrillator (ICD) are often inevitable. In rare cases, a heart-lung-transplantation may be performed. (Schumacher et al., 2008)

## 1.2 Adolescents and adults with CHD

### 1.2.1 Epidemiology

Since the 1940s, great advancements have been achieved in the medical care of patients with CHD, primarily in the field of cardiac surgery, catheter intervention as well as non-invasive diagnosis and intensive care. As a result, mortality rates have markedly decreased and the age of death has shifted from infancy towards adulthood. (Khairy et al., 2010) The survival rate for CHD has risen from approximately 20% in the 1940s to 85% in the 2000s, leading to an increase in the overall prevalence, especially with regard to the adult population (Warnes et al., 2001). This rise of prevalence is particularly pronounced in patients with severe CHD (Marelli, Mackie, Ionescu-Ittu, Rahme, & Pilote, 2007). In developed countries, adults with CHD have probably outnumbered children (Marelli et al., 2014). Although the exact prevalence of the adult population with CHD is not known, the best estimates suggest a prevalence of approximately 3,000 per million (van der Bom, Bouma, Meijboom, Zwinderman, & Mulder, 2012), with significant regional variations due to discrepancies in both incidence and mortality (Mulder, 2012).

In Germany, about 90% of the ca. 6,000 children born with CHD each year reach adulthood. The total number of patients with CHD is increasing, with approximately 200,000-300,000 living in Germany today. The estimated number of adults amongst them is over 120,000. (Kaemmerer & Hess, 2005)

There are two main types of adults with CHD. On the one hand, there is the group of "natural survivors" who reached adulthood without requiring any specific treatment. This group includes both patients with defects that had not been detected earlier and patients with CHD that was detected during childhood but did not need surgery/ intervention or did not receive any due to feasibility or other reasons. The second and larger group consists of patients who underwent cardiac surgery during childhood. (Kaemmerer & Hess, 2005)

### 1.2.2 Health-care considerations in adolescents and adults with CHD

Grown-up patients with CHD consist of a continuously aging population with relatively low mortality but substantial morbidity (Engelfriet et al., 2005). Interestingly, mortality and morbidity are overall higher in males with CHD compared to females (Engelfriet & Mulder, 2009). It is estimated that approximately half of the adults with CHD is at

moderate to high-risk for complications, re-operation or premature death (Warnes et al., 2001).

There is a wide range of health-related issues affecting this specific patient population and needing to be adequately addressed by physicians and health-care professionals involved in their management. An overview is presented in Table 5.

**Table 5: Health-care considerations in the management of adolescents and adults with CHD**

| Medical | Other |
|---|---|
| Health problems directly associated with CHD | Pregnancy and contraception |
| Cardiovascular comorbidities | Social impairment |
| Non-cardiovascular comorbidities | Exercise tolerance and sports participation |
| Psychological impairment | Education and career choice |
| Transition into the adult health care system | Health/ life/ disability insurance, pension |

Adolescents and adults with CHD often face **health problems directly associated with their CHD** and have to deal with lifelong residuals even after repair of their underlying condition. Surgery or interventional treatment may also be required in cases of residual or new hemodynamic complications after prior repair or palliation as well as in cases not diagnosed in childhood or not considered severe enough to require surgery in childhood. (Baumgartner et al., 2010; Engelfriet et al., 2005)

Moreover, the prevalence of further **cardiovascular comorbidities** increases with age. In older patients with CHD, outcome is greatly affected by acquired cardiac conditions, which patients with CHD are especially prone to develop. For example, coronary artery disease may be promoted by several CHD-associated factors such as anomalies of the coronary arteries like in ccTGA or residual defects of the coronary arteries due to manipulation during surgery. (Triedman & Newburger, 2016; Tutarel, 2014)

Concurrently, increasing age also leads to a higher prevalence of **non-cardiovascular comorbidities** that may affect patient outcome. For example, surgical and anesthesia management may be especially challenging in patients with moderate and severe CHD that require non-cardiac surgery. Issues that may arise include cessation of anticoagulation, antibiotic prophylaxis for endocarditis and anesthesia considerations with regard to arrhythmias, pulmonary vascular disease or generally

the functional class of the patient. Therefore, non-cardiac procedures should ideally be performed in centers where physicians experienced in the management of grown-ups with CHD are present. (Baehner & Ellerkmann, 2017; Foster et al., 2001; Warner, Lunn, O'Leary, & Schroeder, 1998)

Since many adolescents and young adults with CHD are sexually active (Reid, Siu, McCrindle, Irvine, & Webb, 2008), the topics **pregnancy and contraception** are particularly relevant, especially for women with complex CHD, and should be adequately addressed by their treating physician (Reid et al., 2008). The risks of pregnancy as well as the recurrence rates of CHD markedly vary depending on the particular condition. Therefore, patients should be well-informed about their individual risks and, if necessary, the available contraception possibilities. (Foster et al., 2001)

Adolescent and adult patients may suffer from psychosocial impairment related to their condition. This should be actively investigated during patient encounters and should lead to early referral to a specialist on mental health, if deemed necessary. Further issues that need to be addressed may be exercise intolerance and sports participation, education and career choice, as well as practical matters for example related to insurance coverage and pension. (Kaemmerer & Hess, 2005)

Due to these potential medical and psychosocial issues, regular follow up is usually required on a life-long basis. Nevertheless, a part of patients with CHD is lost to follow up. This often occurs in the so-called “transitional period”, i.e. the time from adolescence to early adulthood. Many adolescent and young adult patients are unaware of the long-term implications of their condition after primary repair in childhood and are at high risk of missing regular follow-up encounters, especially in the absence of symptoms. Therefore, it is critical that children and adolescents with CHD are comprehensively educated about their condition and encouraged to responsibly take charge of their own health, in order to effectively transition into the adult health care system later. (Foster et al., 2001; Webb, 2001) It is evident that the unique and complex health-care needs of grown-ups with CHD require medical management by physicians with expertise in this particular patient population. For this reason, a certification for physicians and clinics specialized in adults with CHD (ACHD) has been established in Germany. Unfortunately, many adult patients have not yet transferred to certified ACHD providers; thus, the quality of their medical care may be compromised. (Helm et al., 2017)

### 1.2.3 Characteristics of adolescents and adults with CHD

In order to address the above mentioned medical and psychosocial issues and provide patients with optimal counseling and care, it is essential that physicians understand the unique characteristics of this particular patient population. For this reason, numerous studies have been conducted in the last decades in order to investigate the sociodemographic and health-associated characteristics of these patients.

Regarding **education and employment**, it has been consistently reported that adults with CHD have less often a higher occupational level, work less often full-time, are more likely to be unemployed, and have a lower income compared to the general population (Opic et al., 2015; Vigl et al., 2011). While some investigators also describe that adults with CHD are less likely to have a scientific educational level (Opic et al., 2015), others report a higher educational level compared to the general population (Ternestedt et al., 2001).

Since **sexual health and partnership** are aspects associated with quality of life, their assessment is particularly relevant in patients with chronic conditions (Vigl et al., 2009). According to literature, adults with CHD report good sexual functioning and satisfaction compared to the general population (Moons et al., 2007; Winter et al., 2010). However, young adults with CHD are less sexually active compared to their healthy peers (Reid et al., 2008; Vigl et al., 2009). Although male patients with CHD do not suffer from increased rates of erectile dysfunction, patients who face such problems report worse mental and physical quality of life and more depressive symptoms (Vigl et al., 2009; Winter et al., 2010). In female patients, a worse functional status and complex or cyanotic defects are associated with later menarche and increased symptoms related to their cardiac defect during sexual activity (Vigl et al., 2010). Regarding partnership, adults with CHD are more likely to live with their parents compared to the general population, while fewer are married or in a relationship (Kokkonen & Paavilainen, 1992; Opic et al., 2015; Utens et al., 1994; Vigl et al., 2011; Winter et al., 2010).

In patients with CHD, consequences of further cardiovascular comorbidities often associated with age (e.g. coronary artery disease) may be particularly impairing. Hence, assessment of **cardiovascular risk factors** is essential in the management of patients with CHD. Compared to the general population, adults with CHD present higher rates of hypertension, diabetes, hyperlipidemia, obesity and metabolic disorder (Deen et al., 2016; Moon et al., 2015; Moons, Van Deyk, Dedroog, Troost, & Budts, 2006). However, this depends on the kind of the underlying defect. Interestingly, cyanotic

patients seem to have a markedly better cardiovascular risk profile (Moon et al., 2015). Adults with CHD are less likely to exhibit tobacco and alcohol abuse, with men smoking more frequently than women (Moon et al., 2015; Moons et al., 2006). Of note, smoking has been implicated as an important risk factor for mortality amongst adults with CHD (Engelfriet et al., 2008).

Existing literature on **physical activity** in this patient population is inconclusive. Some studies demonstrate that adults with CHD are generally physically active and possibly exercise even more than the general population (Moons et al., 2006; Muller, Hess, & Hager, 2012a) . On the contrary, others report that adults with CHD exercise less than their healthy counterparts (Moon et al., 2015; Opic et al., 2015). It is noteworthy that physical activity is associated with better exercise capacity (Muller et al., 2017a; Muller et al., 2012a) and is considered to be protective against hopelessness (Eslami, Kovacs, Moons, Abbasi, & Jackson, 2017). Some studies also suggest a lower activity level to be associated with a worse physical and mental quality of life (Bay et al., 2017; Muller et al., 2017a), albeit others report no association (Dulfer, Helbing, Duppen, & Utens, 2014; Muller et al., 2012a).

Adults with CHD are reported to have better **emotional and social functioning** compared to the general population. More specifically, they demonstrate less neuroticism, social inadequacy, and hostility, as well as higher self-esteem (Opic et al., 2015, 2016; Utens et al., 1994). Regarding **cognitive functioning**, patients with CHD face limitations, such as confusion, memory loss, or difficulty making decisions, more frequently compared to patients without CHD (Farr, Oster, Simeone, Gilboa, & Honein, 2016).

Although adults with CHD suffer more from somatic symptoms , the prevalence of **anxiety, hopelessness and depression** amongst them is at least comparable, if not lower, than that of healthy individuals (Eslami et al., 2017; Eslami, Sundin, Macassa, Khankeh, & Soares, 2013; Farr et al., 2016; Luyckx et al., 2016; Muller, Hess, & Hager, 2012b, 2013). However, some diagnostic subgroups such as Fontan-patients may be more depressed than their healthy peers (Pike et al., 2012). According to literature, factors associated with anxiety and/or depression are somatic symptoms, financial strain, lack of social support as well as older age and a worse functional status (Amedro et al., 2016a; Eslami et al., 2013; Moon et al., 2009). On the other hand, the main factors preventive of depression are affectionate parental attitude in adolescents and higher resilience (Eslami et al., 2013; Luyckx et al., 2016). Of note, even though uncommon, the presence of anxiety and even minor depressive symptoms in

patients with CHD is associated with lower quality of life and potentially also with decreased exercise capacity (Amedro et al., 2016a; Dulfer et al., 2014; Luyckx et al., 2016; Muller et al., 2012b, 2013; Pike et al., 2012).

Interestingly, major differences in emotional functioning and psychopathological problems have been reported between transatlantic regions (Kovacs, Sears, & Saidi, 2005). While studies conducted in Europe generally report good emotional functioning and fewer psychopathological problems in patients with CHD as mentioned above, studies conducted in the United States demonstrate less favorable results (Brandhagen, Feldt, & Williams, 1991; Bromberg, Beasley, D'Angelo, Landzberg, & DeMaso, 2003; Horner, Liberthson, & Jellinek, 2000).

HRQoL and exercise capacity of adolescents and adults with CHD are extensively discussed below (sections 1.3.3 and 1.4.5).

## 1.3 Health-related quality of life (HRQoL)

### 1.3.1 Definitions

Quality of life (QoL) and HRQoL are two widely used patient-reported outcomes (PRO), i.e. health outcomes directly reported by the patient and thus reflecting the patient's point of view.

The concept of QoL has been extensively discussed in the medical literature for the last few decades, since life expectancy rose due to advancements in medical management and the centrality of the patient's point of view in medical care outcomes was recognized. Defining QoL and HRQoL has proven to be rather challenging, with no single definition available yet. (Karimi & Brazier, 2016)

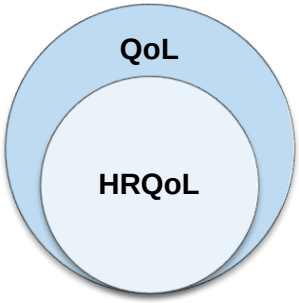
**QoL:**

One of the most widely accepted and comprehensive definitions is the one proposed by the World Health Organization (WHO) that defines QoL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment" (WHO, 1995). This definition implicates that QoL is a multi-dimensional and subjective construct. Others support that QoL should also include objective factors (Karimi & Brazier, 2016), defining QoL for example as "an overall general well-being that comprises objective descriptors and subjective evaluations of physical, material, social, and emotional well-being together with the extent of personal development and purposeful activity, all weighted by a personal set of values" (Felce & Perry, 1995).

**HRQoL:**

HRQoL is a concept which was introduced later and focuses on the aspects of QoL associated with an individual's state of health (Figure 1). Similarly to QoL, there is no single definition for HRQoL. A commonly used definition encompasses "those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment" (Ebrahim, 1995).

**Figure 1: Quality of life (QoL) and health-related quality of life (HRQoL)**



Some critics argue, however, that this definition may not allow for a clear distinction between HRQoL and QoL, since disease and treatment can theoretically affect almost all aspects of QoL to some extent (Karimi & Brazier, 2016). In practice, only aspects directly affected by health are usually considered in HRQoL assessments (eg. social functioning), while others that may not be as strongly affected by disease and treatment are usually not (eg. environmental factors). Other definitions of HRQoL are aslo available, however they resemble more a patient's self-reported health status rather than QoL (Karimi & Brazier, 2016). Such an example is the description by Torrance et al.: "Health-related quality of life includes only those factors that are part of an individual's health" (Torrance, 1987).

### 1.3.2 Assessment of HRQoL

As mentioned in Section 1.3.1., HRQoL is a PRO that incorporates multiple dimensions affected by an individual's state of health. Therefore, measuring HRQoL typically requires multi-item instruments, i.e. questionnaires, that are able to comprehensively cover these domains (Guyatt, Feeny, & Patrick, 1993).

There are several types of PRO instruments used to measure HRQoL, which can be classified according to the measurement approach of the investigated concept. There are two main categories of PRO instruments (Guyatt et al., 1993):

- **generic instruments** (can be used across all populations regardless of age, disease, treatment group etc.) and
- **specific instruments** (focus on a specific patient/ disease group, QoL dimension etc.).

Among the most commonly used specific instruments are disease-specific instruments that are designed to capture domains especially relevant in patients with a specific health condition, such as CHD. Disease-specific HRQoL instruments may include items referring to disease-specific symptoms; yet, they aim to evaluate the effect of these symptoms on QoL domains, thus not being a simple assessment of symptomatology or health status.

A wide range of both generic and specific instruments are being used in clinical studies in the field of CHD. The choice of the appropriate instrument largely depends on the aims of the investigator, with often more than one instruments being combined in a single study (Guyatt et al., 1993). Table 6 presents an overview of instruments used

in adult patients with CHD based on two comprehensive review studies in this patient population (Apers, Luyckx, & Moons, 2013a; Fteropoulli et al., 2013).

**Table 6: HRQoL instruments used in adult patients with CHD**

| Generic | Disease-specific |
|---|---|
| Short Form-36 Health Survey (SF-36) | TNO-AZL* Questionnaire for Adult's Health-related Quality of Life - Congenital Heart Disease version (CHD-TAAQOL) |
| TNO-AZL* Questionnaire for Adult's Health-related Quality of Life (TAAQOL) | |
| Brief World Health Organization Quality of Life assessment (WHOQOL-Bref) | |
| Sickness Impact Profile (SIP) | |
| EuroQOL EQ-5D (preference-based) | |
| Linear Analogue Scale (LAS; one-item) | |
| Satisfaction with Life Scale (SWLS; one-item) | |

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### 1.3.3 HRQoL in adolescents and adults with CHD

Although extensive research has been conducted in this field, literature on the HRQoL of patients with CHD compared to the general population has been inconclusive. Some researchers report worse HRQoL, especially with regard to the physical domains and general health perception but usually not the psychosocial domains (Amedro et al., 2016a; Bruto, Harrison, Fedak, Rockert, & Siu, 2007; Cotts, Malviya, & Goldberg, 2012; Eslami, Macassa, Sundin, Khankeh, & Soares, 2015; Farr et al., 2016; Gierat-Haponiuk, Haponiuk, Chojnicki, Jaworski, & Bakula, 2011; Gratz et al., 2009; Hager & Hess, 2005; Kamphuis et al., 2002; Lane, Lip, & Millane, 2002; Simko & McGinnis, 2003; Vigl et al., 2011). On the contrary, multiple other investigators report comparable or even better HRQoL in patients with CHD, especially with regard to the psychosocial components (Gersony et al., 1993; Gorler et al., 2011; Immer, Althaus, Berdat, Saner, & Carrel, 2005; Loup et al., 2009; Opic et al., 2015, 2016; Pike et al., 2012; Saliba et al., 2001; Silva et al., 2011; Teixeira et al., 2011). This inconsistency may be explained by methodological differences such as the age of the study subjects or by regional variability, since inter-country variations of QoL have been well documented (Moons et al., 2018).

The often favorable HRQoL reported in adolescents and adults with CHD may be explained to some extent by coping mechanisms patients have developed during childhood. The **sense of coherence** is a central concept in the salutogenic model of health by Antonovsky. It is a psychological resource that encompasses the elements comprehensibility, manageability, and meaningfulness and is considered to promote health and well-being. (Antonovsky, 1987) Sense of coherence is reported to be associated with better QoL in patients with CHD (Apers et al., 2015; Apers et al., 2013b; Luyckx et al., 2012; Muller, Hess, & Hager, 2014c; Neuner et al., 2011), while it is only weakly associated with exercise capacity (Muller et al., 2014c). Since patients with CHD have a high sense of coherence, this could explain a favorable QoL despite functional limitations in this patient group (Muller et al., 2014c). Of note, factors potentially associated with an enhanced sense of coherence in adolescents with CHD are better school functioning and fewer cognitive impairments (Apers et al., 2013b).

Knowledge of the factors contributing to HRQoL is crucial in the effort to improve health-care outcomes in patients with CHD. Numerous studies in various countries have examined the relationship of sociodemographic and health-associated factors with HRQoL, with however partly inconclusive results (Apers et al., 2013a; Fteropoulli et al., 2013). Table 7 presents a schematic overview of factors associated with favorable vs. poor HRQoL in adolescents and adults with CHD.

**Table 7: Factors associated with favorable (+) vs. poor (-) HRQoL in adolescents and adults with CHD**

| + | + / - | - |
|---|---|---|
| High educational level and academic performance | Female sex | Arrhythmias, presence of implantable cardioverter defibrillator |
| Social support | Age | Cyanosis |
| Parental support in adolescents | Severity of CHD | Psychosocial impairments, anxiety and depression |
| Religiousness | Prior cardiac surgery | Cognitive impairments |
| Physical activity | | Presence of clinical symptoms |
| High exercise capacity | | Physical limitations, poor functional status |
| Employment | | Unemployment |

There are several factors that have been associated with **favorable HRQoL** overall or with regard to specific domains. These include higher educational level and academic performance, employment, social support, parental support in adolescents, as well as religiousness. Physical activity and high exercise capacity have also demonstrated a positive association with HRQoL, primarily with regard to its physical domains (Bang et al., 2013; Fteropoulli et al., 2013; Luyckx et al., 2012; Muller et al., 2012a; Saliba et al., 2001; Teixeira et al., 2011; Vigl et al., 2011).

At the same time, there is a series of factors that have been implicated to have an association with **poor HRQoL.** These include cardiac conditions such as arrhythmias, presence of implantable cardioverter defibrillator (ICD) and cyanosis (inconsistently and mainly with regard to physical domains), as well as physical limitations, poor functional status, and the presence of clinical symptoms. Cognitive and psychosocial impairments, anxiety and depression, negative thoughts, recent stressful events, as well as unemployment are also factors negatively associated with HRQoL. (Amedro et al., 2016a; Bertoletti et al., 2015; Bratt, Luyckx, Goossens, Budts, & Moons, 2015; Bruto et al., 2007; Irtel et al., 2005; Moons et al., 2018; Opic et al., 2012; Rietveld et al., 2002; Saliba et al., 2001; Silva et al., 2011; Teixeira et al., 2011; Vigl et al., 2011)

Literature on the relationship of **sex and age** with HRQoL is inconsistent. In some studies**,** female sex has been associated with poor HRQoL mainly with regard to its mental components (Amedro et al., 2016a; Vigl et al., 2011), while others contradict these findings reporting no difference between the two sexes (Silva et al., 2011; Teixeira et al., 2011). While some authors report an association between older age and favorable HRQoL (Silva et al., 2011), others report worse HRQoL in older patients (Cotts et al., 2012; Muller et al., 2014a; Vigl et al., 2011) or no association at all (Teixeira et al., 2011).

Similarly, available literature reports conflicting results with regard to the relationship between the **severity of the patient's condition** and HRQoL. Although some studies report no association (DeMaso et al., 2004; Rietveld et al., 2002; Silva et al., 2011; Teixeira et al., 2011; Ternestedt et al., 2001), several others indicate that more complex defects are associated with poorer HRQoL, primarily with regard to its physical components and general health perception (Bratt et al., 2015; Drakouli et al., 2015; Fteropoulli et al., 2013; Kahr et al., 2015; Muller, Hess, & Hager, 2011a; Opic et al., 2016; Simko & McGinnis, 2005; Vigl et al., 2011). Since the presence of symptoms is negatively associated with HRQoL in patients with CHD, this might explain why patients with more severe defects often present poorer HRQoL (Bertoletti et al., 2015;

Schoormans et al., 2013). On the contrary, the specific CHD diagnosis has been consistently shown to have no association with HRQoL (Apers et al., 2013a; Bertoletti et al., 2015).

Literature on the HRQoL of adolescents and adults with CHD with **prior cardiac surgery** is also inconclusive. Some studies demonstrate favorable HRQoL (Bertoletti et al., 2015; Gorler et al., 2011; Immer et al., 2005; Loup et al., 2009), while others report poor HRQoL in previously operated patients (Cotts et al., 2012; Gierat-Haponiuk et al., 2011; Kamphuis et al., 2002; Lane et al., 2002; Teixeira et al., 2011). Interestingly, a cross-sectional study conducted in the United Kingdom reported that among operated patients those deemed surgically cured (eg. prior ASD repair) demonstrated worse overall HRQoL as compared to palliated patients (Lane et al., 2002). A potential explanation for this observation could be a higher sense of coherence in the latter patient group.

## 1.4 Exercise capacity

### 1.4.1 Definition and physiology of exercise

Sport performance encompasses a combination of several elements, such as psychology, tactic and technique, environmental factors, strength, coordination, flexibility and endurance, to a variable extent depending on the type of exercise or sport (Smith, 2003). For instance, psychological and mental factors that may play a significant role in sport performance include team spirit, focus and discipline. Tactic and technique depend not only on training but also on the cognitive abilities of the athlete and trainer as well as their interpersonal communication. Strength is mainly representative of the individual's muscle mass and performance, while endurance usually represents an individual's pulmo-cardio-vascular-muscle performance, typically limited by the cardiovascular system, therefore often described as "cardiovascular fitness".

Formally, exercise capacity can be described as "the maximum amount of physical exertion that a patient can sustain. An accurate assessment of exercise capacity requires that maximal exertion is sufficiently prolonged to have a stable (or steady state) effect on the circulation and that the pattern of patient response is consistent when exertion is repeated." (Goldstein, 1990) Several physiologic factors contribute to an individual's exercise capacity, including cardiovascular performance, pulmonary gas exchange, as well as tissue metabolism (Albouaini, Egred, Alahmar, & Wright, 2007). Assessment of exercise capacity, which has both diagnostic and prognostic value in adults with CHD, is typically performed with cardiopulmonary exercise testing (CPET) (Mantegazza, Apostolo, & Hager, 2017). In the absence of pulmonary or muscular/metabolic disease, CPET measures mainly endurance capabilities, i.e. "cardiovascular fitness".

There are several forms of exercise that can be characterized based on the type of muscle activity involved. With regard to mechanical aspects, exercise can be characterized as dynamic (isotonic) with limb movement or static (isometric) without limb movement. From a metabolic point of view, exercise can be aerobic when oxygen is available for metabolic processes or anaerobic in the absence of oxygen. For example, endurance exercise, which is usually applied in exercise testing, is a form of dynamic-aerobic exercise. (Fletcher et al., 2013)

In healthy subjects, exercise leads to an increased demand for oxygen primarily in skeletal muscle. Cardiovascular responses are set in action to accommodate this de-

mand by increasing oxygen uptake in the muscles. Heart rate (HR) and stroke volume (SV) gradually increase during exercise, thus leading to an increase in cardiac output (CO). However, SV reaches a plateau at about 50-60 % of maximal exertion, with HR being the main driver of CO increase beyond this point. CO can reach levels up to a 4-fold to 6-fold above rest during strenuous exercise in an upright position. (Fletcher et al., 2013)

After initiation and during mild-to-moderate intensity exercise, energy in muscle tissue is generated through aerobic metabolic pathways with the use of oxygen. After approximately 3-5 minutes of exercise at this intensity, steady-state conditions, with practically constant HR, CO, blood pressure (BP) and pulmonary ventilation, are usually reached. With increasing intensity towards maximal effort, working musculature is not able to derive all energy from oxygen utilization anymore and anaerobic metabolic pathways are activated. During moderate-to-high intensity exercise above this "anaerobic threshold", a stimulation of the sympathetic nervous system with parallel inhibition of the parasympathetic nervous system lead to an increased blood flow and oxygen consumption in skeletal muscle. Thus, total peripheral resistance decreases. (Fletcher et al., 2013)

The maximal oxygen uptake that can be achieved during exercise can be calculated as the product of maximum CO and maximum arteriovenous oxygen difference. (Fletcher et al., 2013)

### 1.4.2 Cardiopulmonary exercise testing (CPET) - Indications/ Contraindications

Prior to CPET, the purpose of the examination should be clearly defined in order to maximize the diagnostic value of the test and to ensure safety (Fletcher et al., 2013). CPET is indicated in numerous conditions and situations, both in the initial evaluation and in follow-up (where applicable), including but not limited to (ATS/ACCP, 2003; Guazzi et al., 2012):

- heart failure, CHD, suspected myocardial ischemia,
- chronic obstructive pulmonary disease, exercise-induced asthma, interstitial lung disease, pulmonary vascular disease,
- suspected mitochondrial myopathy,
- preoperative assessment (e.g. prior to lung resection surgery), and
- assessment of functional impairment. (ATS/ACCP, 2003; Guazzi et al., 2012)

After determination of the indication, thorough clinical evaluation of the patient should be performed in order to detect any potential risks that would constitute a contraindication for testing.

More specifically, all patients must undergo following assessments prior to CPET:

- medical history including current medications,
- physical examination including auscultation of the heart and lungs,
- 12-lead ECG at rest, and
- blood pressure (BP) measurement at rest.

Potential contraindications include acute or severe disorders of the cardio-respiratory or any other organ system as well as any condition hindering adequate and safe physical exercise. Some examples of CPET **contraindications** are listed below (absolute contraindications in bold) (Fletcher et al., 2013; Hager & Hauser, 2007):

Cardiac disease

- **Acute endocarditis**, **myocarditis, or pericarditis**
- **Symptomatic severe aortic stenosis**
- **Hemodynamically relevant cardiac arrhythmia**
- **Decompensated congestive heart failure**

Vascular Disease

- **Acute myocardial infarction**, **unstable angina**
- **Acute pulmonary embolism or deep vein thrombosis**
- **Acute aortic dissection**/ aortic aneurysm
- Resting hypertension >200/120 mmHg
- Recent stroke/ transient ischemic attack

Other

- Acute severe infections, uncorrected anemia or hyperthyroidism
- Mental or **physical impairment precluding safe and adequate physical exercise**

(Fletcher et al., 2013; Hager & Hauser, 2007)

### 1.4.3 Cardiopulmonary exercise testing (CPET) -Procedures

CPET should be performed under **standardized laboratory conditions** (room temperature 16–24°C, humidity 30–60%) in order to achieve reliable and comparable results. There are several types of equipment that can be used for exercise testing, with the most common being **treadmill and cycle ergometers**. Other devices such as arm ergometers are also available but are rarely used in clinical practice. Treadmill ergometers are generally more common in the United States, while in Europe cycle ergometers are usually preferred. (ATS/ACCP, 2003; Fletcher et al., 2013; Lollgen & Leyk, 2018)

As shown in Table 8, both methods have a different spectrum of advantages and disadvantages, which may guide the decision on equipment choice.

**Table 8: Cardiopulmonary exercise testing with treadmill vs. cycle ergometer**

| | Treadmill | Cycle |
|---|---|---|
| **Advantages*** | ➢ Activates a larger muscle mass, generating 5-10% higher peak oxygen uptake<br>➢ No special training experience needed | ➢ Probably safer<br>➢ Lower cost<br>➢ Higher practicability: smaller, less noisy, less artifacts of BP-measurement and ECG recording due to less upper body motion, easier blood gas collection |
| **Disadvantages*** | ➢ Not suitable for patients with ambulatory difficulty (e.g. gait imbalance, orthopedic disorders, severe obesity)<br>➢ Insecurity due to the moving surface | ➢ Earlier leg muscle fatigue in inexperienced subjects may lead to early test termination |

**(ATS/ACCP, 2003; Fletcher et al., 2013; Lollgen & Leyk, 2018)*

In order to ensure **patient safety**, close monitoring of the patient should be performed during exercise and shortly after. More specifically, continuous pulse oximetry and ECG monitoring, as well as frequent BP measurements every one to two minutes are required to allow for early test termination in case of complications. Although CPET is considered to be a generally safe examination, life-threatening events like myocardial infarction or severe arrhythmias and even death may occur. (Lollgen & Leyk, 2018; Myers, Voodi, Umann, & Froelicher, 2000)

Standardized **testing protocols** should be applied in all institutions and laboratories, in order to generate comparable CPET results. This is particularly important for monitoring individual patients over time as well as for comparisons between different patients and patient groups. (Lollgen & Leyk, 2018) There are several types of protocols with both treadmill and cycle ergometer that can be classified according to the way the work rate is applied. Incremental protocols with progressively increasing work rate are most commonly used in clinical practice. A typical maximal incremental testing protocol includes an initial warm-up phase, followed by exercise with gradual increase of work rate (at specific time intervals or continuously in a ramp-like fashion). After reaching the point of maximal exertion or the test is terminated by the supervisor, a recovery period at low workload follows in order to prevent a rapid drop of blood pressure. Constant work load protocols, where the patient exercises at a constant work rate for at least 6 minutes, are currently gaining popularity due to their applicability in monitoring the response to various interventions. (ATS/ACCP, 2003) After the exercise phase, patients should be observed for several minutes at rest, since there is a relatively high incidence of arrhythmias and hypotension observed shortly after exercise (Fletcher et al., 2013; Lollgen & Leyk, 2018).

### 1.4.4 Cardiopulmonary exercise testing measurements

Numerous parameters can be assessed during exercise testing, with greatest value when exercise is conducted at maximal effort. Except from subjective symptoms like dyspnea and chest discomfort caused by exercise, these may include following objective measurements (ATS/ACCP, 2003; Mantegazza et al., 2017):

- HR, BP, ECG
- Blood gas analysis (BGA), lactate
- Work rate (WR): performance achieved in Watt
- Ventilatory: respiratory rate (RR), respiratory minute ventilation ($\dot{V}E$), tidal volume (Vt), $O_2$ pulse (ratio between oxygen uptake ($\dot{V}O_2$) and HR)
- Metabolic gas exchange:
  - Peak $\dot{V}O_2$: “Highest oxygen uptake in a 30-s period during exercise.” (Mantegazza et al., 2017) Best single indicator of cardiopulmonary function in patients with CHD.
  - Respiratory exchange ratio (RER): Ratio between carbon dioxide output ($\dot{V}CO_2$) and $\dot{V}O_2$. Depends on the metabolic pathways used for energy generation (e.g. carbohydrates, fat). Reflects exercise effort. At maximal effort, RER

>1.1

  - Ventilatory threshold (VT): $\dot{V}O_2$ at the point of exercise at which $\dot{V}CO_2$ increases disproportionately to $\dot{V}O_2$ because of additional activation of anaerobic metabolic pathways

- Pulmonary gas exchange:
  - $\dot{V}E/\dot{V}CO_2$: Ventilatory equivalent of $CO_2$. “Represents the cost of carbon dioxide elimination in terms of ventilation.”(Mantegazza et al., 2017)
  - $\dot{V}E/\dot{V}CO_2$ slope: Slope of $\dot{V}E$ (y-axis) and $\dot{V}CO_2$ (x-axis) during incremental exercise. Reflects pulmonary ventilation-perfusion match.
  - $\dot{V}E/\dot{V}O_2$: Ventilatory equivalent of $O_2$. “Represents the cost of oxygen uptake in terms of ventilation.”(Mantegazza et al., 2017)
  - End-tidal oxygen pressure ($P_{ET_{O2}}$): Used in relation to arterial oxygen pressure to detect lung diffusion defects or ventilatory dead space.
  - End-tidal $CO_2$ pressure ($P_{ET_{CO2}}$): Used in relation to arterial $CO_2$ pressure. Reflects ventilation-perfusion match in the pulmonary circulation.

(ATS/ACCP, 2003; Mantegazza et al., 2017)

### 1.4.5 Exercise capacity in adolescents and adults with CHD

Generally, grown-up patients with CHD have been consistently reported to exhibit diminished exercise capacity compared to their healthy counterparts (Bruto et al., 2007; Buys et al., 2011; Gratz et al., 2009; Lemmer et al., 2011).

The extent of their exercise limitations largely depends on the severity of their underlying cardiac condition. Generally, patients with cyanotic and/or complex lesions such as UVH or Ebstein’s anomaly experience aggravated deficits of their exercise tolerance, with patients with Eisenmenger syndrome being the most compromised subgroup (Buys et al., 2011; Diller et al., 2005; Foster et al., 2001; Kempny et al., 2012; Muller et al., 2011a). Of note, patients that underwent complete repair demonstrated better exercise capacity compared to patients with significant anatomic residua (Rosenblum, Katz, Reuveny, Williams, & Dubnov-Raz, 2015). Patients with simpler defects, such as ASD, VSD or valvular defects, have been reported to experience better -but still subnormal- exercise capacity (Foster et al., 2001; Kempny et al., 2012).

Despite having an objectively diminished exercise capacity, adults with CHD often report good physical functioning, overestimating their physical capabilities. Available

literature is indicative of an association between exercise capacity and HRQoL in adults with CHD; however, it is usually weak and predominantly related to its physical domains (Amedro et al., 2016b; Dulfer et al., 2014; Gratz et al., 2009; Hager & Hess, 2005; Irtel et al., 2005; Lemmer et al., 2011; Muller et al., 2011a). In adolescents and adults with CHD, this distorted perception of their limitations may be explained by life-long adaptation to a compromised functional status (Mantegazza et al., 2017).

# 2 Problem outline and hypothesis

Adolescents and adults with CHD are a constantly growing population with unique medical and psychosocial characteristics. While their mortality is generally low, they often suffer from substantial morbidity due to lifelong residuals even after correction/repair in childhood. Therefore, the key measure for the evaluation of health-care outcomes in these patients is not only mortality anymore, but also other variables associated with functional health.

As the therapeutic possibilities available for adolescents and adults with CHD are expanding, the effectiveness of the various treatment options needs to be thoroughly evaluated, with functional variables such as HRQoL and exercise capacity serving as the main endpoints. As mentioned in section 1, to date research has not yet adequately addressed this need. With a few exceptions (Mohr et al., 2014; Muller et al., 2014b; Penha et al., 2015), existing studies in patients with CHD are mostly cross-sectional, thus not allowing us to draw solid conclusions regarding the actual effects of the different therapeutic options. Moreover, the majority of treatment studies focus on children with CHD. However, children differ significantly from their adult counterparts with regard to cardiac defect pathophysiology, co-morbidities as well as cognitive and emotional functioning. Lastly, existing studies usually investigate a single treatment method, mostly a specific surgical or interventional procedure (Bertoletti et al., 2015; Heusch et al., 2014; Latal et al., 2009; Loup et al., 2009; Muller et al., 2009; Muller et al., 2014b; Muller et al., 2011b). Taken together, our understanding regarding the effectiveness of the various treatment options in terms of changes in functional health in adolescents and adults with CHD remains incomplete.

Taking into account published data indicating that specific interventional/surgical procedures are associated with improvement of HRQoL in patients with a specific cardiac defect (Mohr et al., 2014; Muller et al., 2014b), we hypothesized that generally heart surgery and catheter intervention are more effective compared to other treatment options with regard to changes in HRQoL over time in adolescents and adults with CHD.

# 3 Methods

## 3.1 Study design

To address our hypothesis, we conducted a **retrospective, longitudinal study** in adolescents and adults with CHD at the Department of Pediatric Cardiology and Congenital Heart Defects of the German Heart Centre Munich ("Deutsches Herzzentrum München") in Munich, Germany.

The objectives of the study were the following:

Primary objective:

- To compare the effectiveness of the four main treatment options, i.e. surgery, catheter intervention, change in medication and no change in treatment, in terms of changes in HRQoL over time,

Secondary objectives:

- To compare the effectiveness of the four main treatment options, i.e. surgery, catheter intervention, change in medication and no change in treatment, in terms of changes in exercise capacity over time, and

- To assess the association between changes in HRQoL and exercise capacity over time.

The overall goal of the study was to serve as an orientation framework to support both physicians and their patients in the shared decision-making process regarding treatment-related matters.

## 3.2 Patients

### 3.2.1 Patient selection

In order to identify eligible patients, the institutional Munich CHD database was reviewed for CPET. This database includes comprehensive demographic and clinical information on patients who were referred for CPET from the tertiary outpatient clinic for CHD. CPET is considered a routine follow-up examination for all patients with moderate and severe CHD in our clinic. Prior to exercise testing, patients routinely complete the German version of the SF-36 questionnaire with a 4-week window on HRQoL. For this study, all patients referred for CPET between June 2001 and June

2016 were reviewed. Patients gave written informed consent. Data collection was completed in June 2016.

Since the endpoints of the study were longitudinal HRQoL and exercise capacity, only patients who had both undergone CPET and completed the SF-36 questionnaire prior to their examination on at least two occasions were eligible. Patients had to be 14 years or older, as the SF-36 questionnaire is only validated in this age group.

Patients who could not fill out the SF-36 questionnaire, either due to lack of German language knowledge or due to limited cognitive ability to understand the questions, were excluded from the study.

In order to ensure accuracy of our findings, we also excluded all patients who did not reach maximal exertion during CPET according to previously described, pre-defined criteria. Criteria of insufficient exercise effort during CPET were oxygen saturation at peak exercise (peak $SpO_2$) ≥ 90% combined with peak heart rate (HR) ≤ 85% and respiratory exchange ratio (RER) ≤ 1.05. Cyanotic patients, defined as $SpO_2$<90% at rest or during exercise, were included in the study regardless of peak HR and RER, since they were generally considered incapable of reaching these values. (Muller, Heck, Ewert, & Hager, 2017b)

For the analysis of data regarding exercise capacity measured as peak $\dot{V}O_2$, some patients had to be excluded due to a change of the CPET equipment in January 2010. More specifically, the CPET laboratory equipment was switched from Vmax 229 to Encore 29 (both Becton Dickinson, Franklin Lakes, NJ, USA). The latter measured slightly higher values of peak $\dot{V}O_2$ (about 5%). Therefore, particularly for the investigation of changes in peak $\dot{V}O_2$, we excluded patients whose baseline examination was before January 2010 and the follow up examination was after that date.

### 3.2.2 Baseline and follow-up examination selection

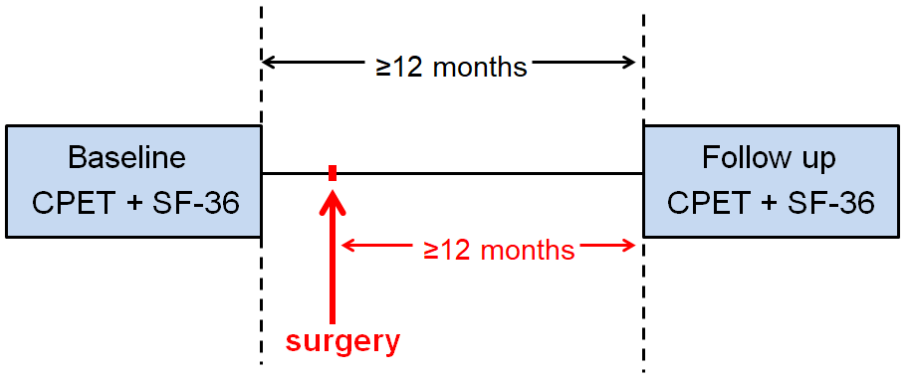
In this longitudinal study, we were interested in the changes of HRQoL and exercise capacity over time. Therefore, two CPET examinations with the associated SF-36 questionnaires were selected per patient. The selection was based on the following pre-defined criteria:

1. The patient had to be 14 years or older at the time of both examinations;
2. Each examination had to be at least 12 months after any previous heart surgery or catheter intervention, in order to avoid the interference of any short-term post-surgical/-interventional complications with our results;

3. The two selected examinations had to be at least 12 months apart.

In cases where more than two examinations per patient met the above criteria, the pair with the longest follow-up time and the higher exertion values during CPET (peak HR and peak RER) was selected. Figure 2 presents a schematic example for the selection of baseline and follow-up examinations.

**Figure 2: Criteria for the examination selection in a patient who underwent surgery** *(CPET=cardiopulmonary exercise testing)*

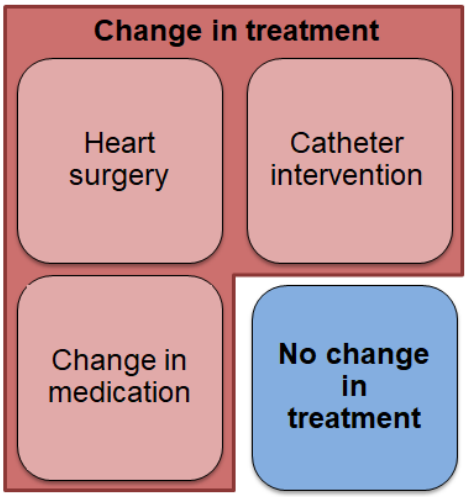



### 3.2.3 Assignment of patients to treatment groups

After selection of the examination pair for each individual patient, their medical history for the time period between baseline and follow up examination was retrospectively reviewed. The main focus of the search was therapeutic interventions and/or changes in the existing therapeutic regimen, with the main source of information being electronic CPET records, surgery or catheter intervention reports, as well as referral and discharge notes. According to the treatment they received between the baseline and follow-up examination, each patient was assigned to one of four treatment groups.

The **four treatment groups** were: “heart surgery“, “catheter intervention”, “change in medication”, and “no change in treatment” (i.e. surveillance). For analysis purposes, the first three treatment groups were summarized in one larger group named **“change in treatment”** as compared to the **“no change in treatment”** group. (Figure 3)

**Figure 3: Treatment groups**




In patients who received more than one of the treatment options during the follow-up time period, heart surgery was considered to outweigh catheter intervention, which in turn outweighed change in medication. Concerning changes in medication, only agents that have a substantial effect on the cardiopulmonary system or the mental health were taken into account. Thus, following agents did not affect the assignment of patients into treatment groups: herbal products, inhaled medications, contraception drugs, supplements (e.g. iron, potassium, magnesium), and antithrombotic agents (e.g. aspirin, heparin, vitamin K-dependent or -independent oral anticoagulation).

### 3.2.4 Categorization according to severity grade

Depending on their condition at baseline, patients' CHD was categorized into three severity grades, namely simple, moderate, and complex, according to the classification of the American College of Cardiology (ACC) by Warnes et al (Warnes et al., 2001). In order to adjust this existing classification to the wide spectrum of our patients, we added some diagnostic groups that were not originally included. More specifically, tricuspid and pulmonary valve regurgitation grade 1-2 were included in the category of simple CHD. Heart valve disease after repair, tricuspid valve regurgitation grade 3-4 and the ALCAPA syndrome were considered CHD of moderate severity. Lastly, patients with pacer or ICD were assigned to the category of complex CHD.

## 3.3 Outcome variables

In line with the objectives of the study (see section 3.1.), we included following outcome variables in our analysis:

- Mean change in the SF-36 physical summary score over time,
- Mean change in the SF-36 mental summary score over time, and
- Mean change in exercise capacity measured as peak $\dot{V}O_2$ during CPET over time.

A detailed description of the methodology applied for the assessment of the three outcome variables is presented in the following subsections (3.3.1 and 3.3.2).

### 3.3.1 The SF-36 survey

The German version of the Medical Outcomes Study 36-item short-form health survey (SF-36) was used to quantitatively assess HRQoL (SF-36 Version 1, New England Hospital Inc., Boston, MA, USA) (Bullinger, 1995; Ware & Sherbourne, 1992).

All patients received the SF-36 questionnaire prior to CPET. They were required to complete it without any external assistance.

**Characteristics and Development**

The SF-36 is a generic PRO instrument for the assessment of HRQoL, which can be used regardless of disease and treatment group in individuals who are 14 years or older (Aaronson et al., 1992). It is one of the most commonly used instruments for HRQoL evaluation in patients with CHD (Kahr et al., 2015), but it is also used in many other specialties.

The SF-36 has its origins in the Medical Outcomes Study (MOS) (Tarlov et al., 1989), which was a large-scale, longitudinal study on PROs and generic health scales for people with chronic conditions in the United States (US). MOS researchers selected and adapted items from several previously used questionnaires and other sources in order to create the 149-item Functioning and Well-Being Profile (FWBP). However, the need for a briefer questionnaire that would nevertheless satisfy the minimum psychometric requirements and standards for comprehensiveness lead to the creation of a short-form questionnaire with 36 items, the SF-36 Health Survey. (Ware & Sherbourne, 1992) The SF-36 items, which were derived from the FWBP, represent 8 of the most important and frequently used health concepts of HRQoL (Ware & Sherbourne, 1992).The International Quality of Life Assessment (IQOLA) Project was

established in 1991 to translate, adapt and validate the U.S. SF-36 Health Survey in several countries (Aaronson et al., 1992), including Germany (Bullinger, 1995).

Psychometric testing of the German version of the SF-36 Survey demonstrated high validity and reliability (Cronbach's a>0.7 for most scales). Furthermore, it revealed high responsiveness and discriminative power in distinguishing populations with different medical conditions. Ordinality with a scale approaching equidistance was shown in the performed Thurstone's test. (Bullinger, 1995)

**Measurement model and scoring**

The SF-36 questionnaire includes a total of 36 questions, which can be answered in approximately 5-10 minutes by choosing one of the two to six response options.

One item of the questionnaire refers to the **self-reported health transition within the last 12 months**. This item has 5 response options that are converted to scores of 0, 25, 50, 75 and 100, respectively. A score of 50 means no change in general health, while higher scores reflect improvement and lower scores worsening. (Bullinger M, 1998)

The remaining 35 of 36 items refer to the patient’s preceding 4 weeks. These items build **8 health scales**, which assess the following health concepts of HRQoL (Ware & Sherbourne, 1992):

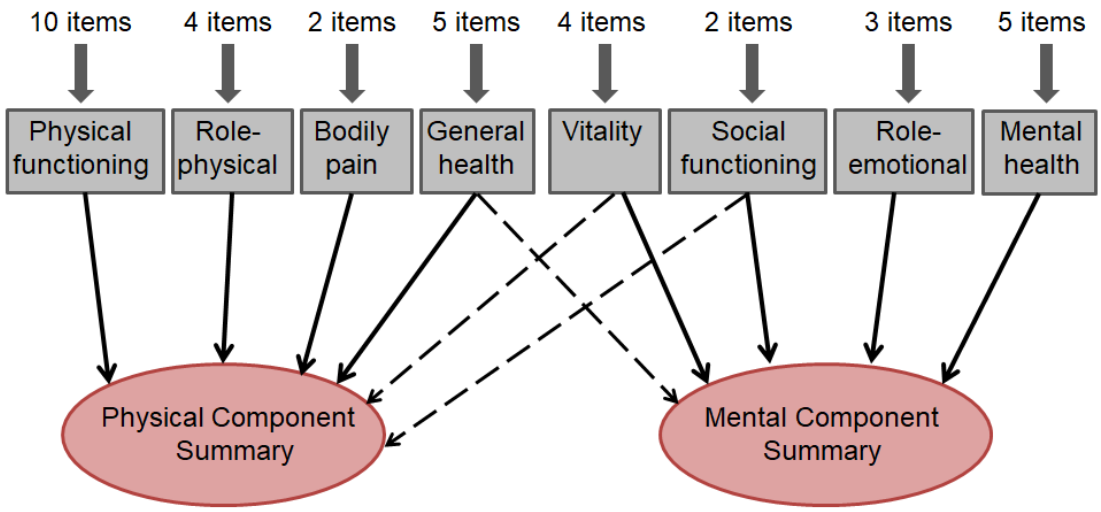
- **Physical functioning** (10 items): evaluates limitations in physical activities (ranging from daily activities such as dressing to vigorous activities) due to health
- **Role-physical** (4 items): evaluates role limitations in daily activities resulting from physical health
- **Bodily pain** (2 items): evaluates limitations due to pain
- **General health** (5 items): evaluates the individual's perception of personal health (ranging from poor to excellent)
- **Vitality** (4 items): evaluates in what extent the individual feels energetic
- **Social functioning** (2 items): evaluates the interference with normal social activities due to physical and emotional issues
- **Role-emotional** (3 items): evaluates role limitations in daily activities resulting from emotional issues

- **Mental health** (5 items): evaluates the mental state of the individual (ranging from feelings of nervousness and depression all of the time to feeling peaceful, happy and calm all of the time).

The 8 health scales finally form two summary measures: the **Physical Component Summary** and the **Mental Component Summary**. All scales contribute to the formation of both summary measures, however to a different extent depending on their level of correlation with the physical and mental health components. More specifically, the scales “physical functioning”, “role-physical” and “bodily pain” contribute most to the Physical Component Summary, while the Mental Component Summary is mostly formed by the scales “mental health”, “role-emotional” and “social functioning”. The scales “general health”, “vitality” and “social functioning” have a substantial contribution to both summary scores. The scores of the two summary scales have a mean value of 50 and a standard deviation of 10. Higher scores mean better and lower scores mean worse HRQoL. (Ware & Gandek, 1998; Ware, Kosinski, & Keller, 1994)

Figure 4 presents a simplified overview of the eight health scales and their main contribution to the formation of the two summary components of the SF-36.

**Figure 4: Simplified schema of the SF-36 health scales and summary components**



### 3.3.2 Cardiopulmonary exercise testing (CPET)

Exercise capacity, which was one of the outcome variables of this study, was measured as peak oxygen uptake (peak $\dot{V}O_2$) during CPET.

In our clinic, CPET is a routine examination in the monitoring of all patients with moderate and severe CHD and is regularly performed to evaluate the development of physical limitations and the patient's general course of disease. Therefore, even though specific indications such as progression of clinical symptoms, treatment decisions and preoperative risk assessment may have been the trigger for a CPET referral in a few individual cases, CPET was performed as a routine follow-up examination in the vast majority of patients included in this study. Patients completed the SF-36 questionnaire prior to CPET.

All patients included in this study underwent a symptom-limited CPET on a cycle ergometer in an upright position, as described previously (Ehlert et al., 2012; Muller et al., 2014b). The examination was conducted according to the following standard incremental protocol:

- 3-minute monitoring at rest
- 3-minute warm-up with unloaded cycling,
- ramp-wise, i.e. steady, increase of load with 5, 10, 15, 20 or 30 W/min (depending on the expected physical capacity of each individual as estimated by the supervising investigator) until the point of physical exertion
- 3 minutes of cool-down with low load cycling, and
- 2 minutes of monitoring during recovery without cycling.

During the examination, ECG and pulse oximetry were monitored continuously, while blood pressure was measured every other minute. The CPET featured a breath-by-breath gas exchange analysis using a metabolic cart. Peak $\dot{V}O_2$ was defined as the highest mean uptake of any 30-second interval during exercise.

Termination of exercise testing was generally determined by the patient due to symptoms of physical exertion such as dyspnea or leg fatigue. The test supervisor encouraged patients to achieve maximum effort during exercise in order to reach physiologic limitation. However, exercise testing was terminated earlier by the medical supervisor in case of complications, including clinical symptoms such as angina or dizziness,

pathologic ECG changes or BP anomalies. (Fletcher et al., 2013; Hager & Hauser, 2007; Lollgen & Leyk, 2018)

## 3.4 Statistical analysis

Data was analyzed with the Statistical Package for Social Sciences (SPSS) version 22.0.1 (SPSS Inc., Chicago, IL, USA), which is a comprehensive statistical analysis tool widely used in the field of social sciences and medical research. Normal distribution of the examined variables was assumed due to the size of the study population. Results were reported as the mean value with the associated standard deviation (mean ± SD), unless otherwise specified.

Descriptive statistics were used for demographic, baseline disease and treatment characteristics. Differences between two values were examined by t-tests (paired or unpaired), while differences between more than two groups were examined by analysis of variance (ANOVA). In order to address our hypothesis, ANOVA comparing the four treatment groups (along with Bonferroni post hoc testing) followed by multiple regression analysis was performed. The association between longitudinal HRQoL and exercise capacity was examined by Pearson's correlation analysis.

A more detailed description of the statistical methods applied is presented in the subsections below (3.4.1-3.4.4).

In all analyses, p-values <0.05 were considered significant.

### 3.4.1 T-test

The t-test is a parametric test commonly used to determine whether the mean values of two samples are significantly different (Kim, 2015b). A t-test can be unpaired, when two independent samples are being compared, or paired. The latter is the case either when the two samples consist of units that have been matched due to their similarity regarding specific characteristics (matched-pairs t-test) or when one group has been tested twice (repeated-measures t-test) (Kim, 2015b).

In this study, paired t-tests were performed to assess whether the changes in HRQoL and exercise capacity over time in the total study population were significant. Unpaired t-tests were used to compare the mean changes in HRQoL and exercise capacity between patients who received active treatment ("change in treatment" group, including heart surgery, catheter intervention and change in medication) and patients on surveillance ("no change in treatment" group).

### 3.4.2 Analysis of Variance (ANOVA) and post hoc testing

ANOVA is a statistical analysis model used to detect differences between the means of groups. It is particularly useful in cases where the means of three or more groups are compared. It should be highlighted that a statistically significant result in ANOVA only reveals that at least one group differs significantly from the others. In order to identify between which particular groups this difference exists, additional **post hoc tests** are usually applied. The Bonferroni test is a widely used post hoc test, which is appropriate for relatively small sets of comparisons typically composed of less than ten contrasts. (Kim, 2015a)

In this study, we performed one-way ANOVAs (followed by Bonferroni post hoc testing) in order to detect differences of the outcome variables between diagnostic groups, grades of severity, and treatment groups.

### 3.4.3 Multivariable regression analysis

Multivariable (or multiple) regression is a statistical tool used to investigate the relationship between two or more independent (or explanatory/predictor) variables and a dependent (or response/outcome) variable.(Hidalgo & Goodman, 2013)

In this study, we performed multivariable regression analyses to investigate the relationship of treatment type and other potential predictors with each one of the three outcome variables. In the applied multivariable model, except for the four treatment options (i.e. surgery, catheter intervention, change in medication, and no change in treatment), we also included variables known or suspected to be associated with longitudinal HRQoL and exercise capacity in patients with CHD. These were: the baseline values of the examined outcome variable, sex, height, body mass, body mass index (BMI), baseline age, presence of pacemaker/ICD (in peak $\dot{V}O_2$ analysis) and follow-up duration.

### 3.4.4 Correlation between HRQoL and exercise capacity

Correlation analysis is used to investigate the presence of a linear association between two continuous variables, with the strength and direction of this linear association being indicated by the correlation coefficient. A higher absolute value of the correlation coefficient represents stronger association between the variables. (Mukaka, 2012)

In this study, the Pearson's correlation coefficient was calculated in order to examine the association between changes in the physical/mental summary scores of HRQoL and changes in peak $\dot{V}O_2$ over time.

# 4 Results

## 4.1 Demographic, baseline disease and treatment characteristics

Based on the patient selection criteria described in section 3.2.1., a total of 1014 patients were included in this study. These patients were included in all analysis concerning HRQoL. For analysis regarding exercise capacity, some of these patients had to be excluded due to a change of the CPET equipment in January 2010, as explained is section 3.2.1. Thus, the number of patients included in analyses concerning changes in peak $\dot{V}O_2$ was reduced to 469 (n=469).

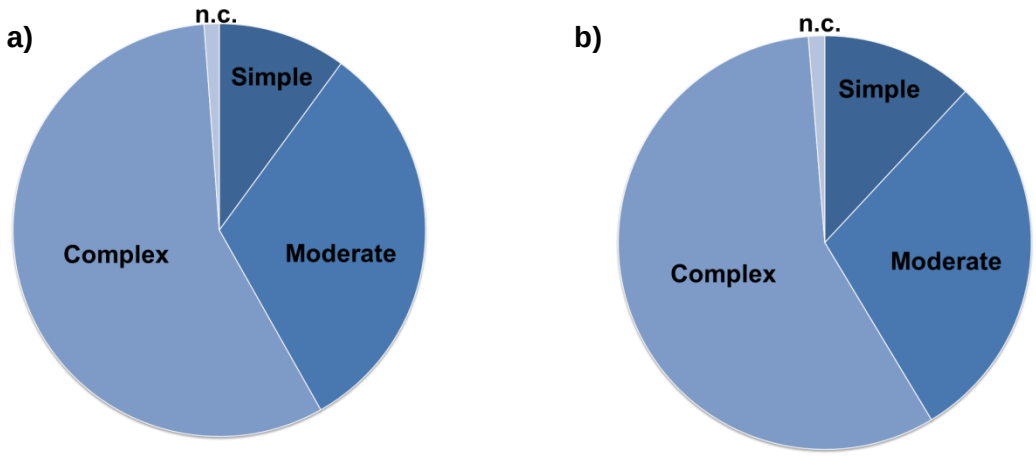
The median age of the total study population was 24 years, with the youngest patient being 14 and the oldest 67 years old. Almost half of the patients were female (43%). The severity grade of the patients' CHD at baseline was variable, with a ratio of approximately 1:3:5 for simple: moderate: complex CHD across the study population. The subgroup of patients included in analyses concerning exercise capacity ("peak $\dot{V}O_2$ study population", n=469) demonstrated similar demographic and baseline disease characteristics to the total study population ("HRQoL study population", n=1014). (Table 9, Figure 5)

**Table 9: Demographic and baseline disease characteristics**

| | HRQoL study population | Peak $\dot{V}O_2$ study population |
|---|---|---|
| **Total patients,** *n* | 1014 | 469 |
| **Sex,** *n (%)* | | |
| Male | 578 (57.0) | 264 (56.3) |
| Female | 436 (43.0) | 205 (43.7) |
| **Baseline age in years** | | |
| Minimum - maximum | 14.1 - 67.3 | 14.1 - 65.0 |
| Median (quartile Q1, Q3) | 24.4 (18.6, 31.7) | 25.4 (19.1, 34.0) |
| **Baseline grade of severity,** *n (%)* | | |
| Simple | 102 (10.1) | 56 (11.9) |
| Moderate | 322 (31.8) | 138 (29.4) |
| Complex | 578 (57.0) | 269 (57.4) |
| Not classified | 12 (1.2) | 6 (1.3) |
| **Follow-up time in years,** *mean ± SD* | 4.0 ± 2.2 | 2.8 ± 1.3 |

*SD= Standard deviation. Note. Adapted from "Effects of Congenital Heart Disease Treatment on Quality of Life", by M. Boukovala, J. Müller, P. Ewert and A. Hager, 2019, The American Journal of Cardiology, 123(7), p. 1163-1168. Copyright 2019 by Elsevier Inc.*

**Figure 5: Baseline severity grades in a) the HRQoL study population and b) the peak $\dot{V}O_2$ study population** *(n.c.=not classified)*



Patients included in our study had a wide spectrum of diagnoses, with the most common diagnostic groups being heart valve disease (n=215), followed by TOF (n=189) and TGA (n=178). A detailed overview of the diagnostic groups in the study population is presented in Table 10 and Figure 6.

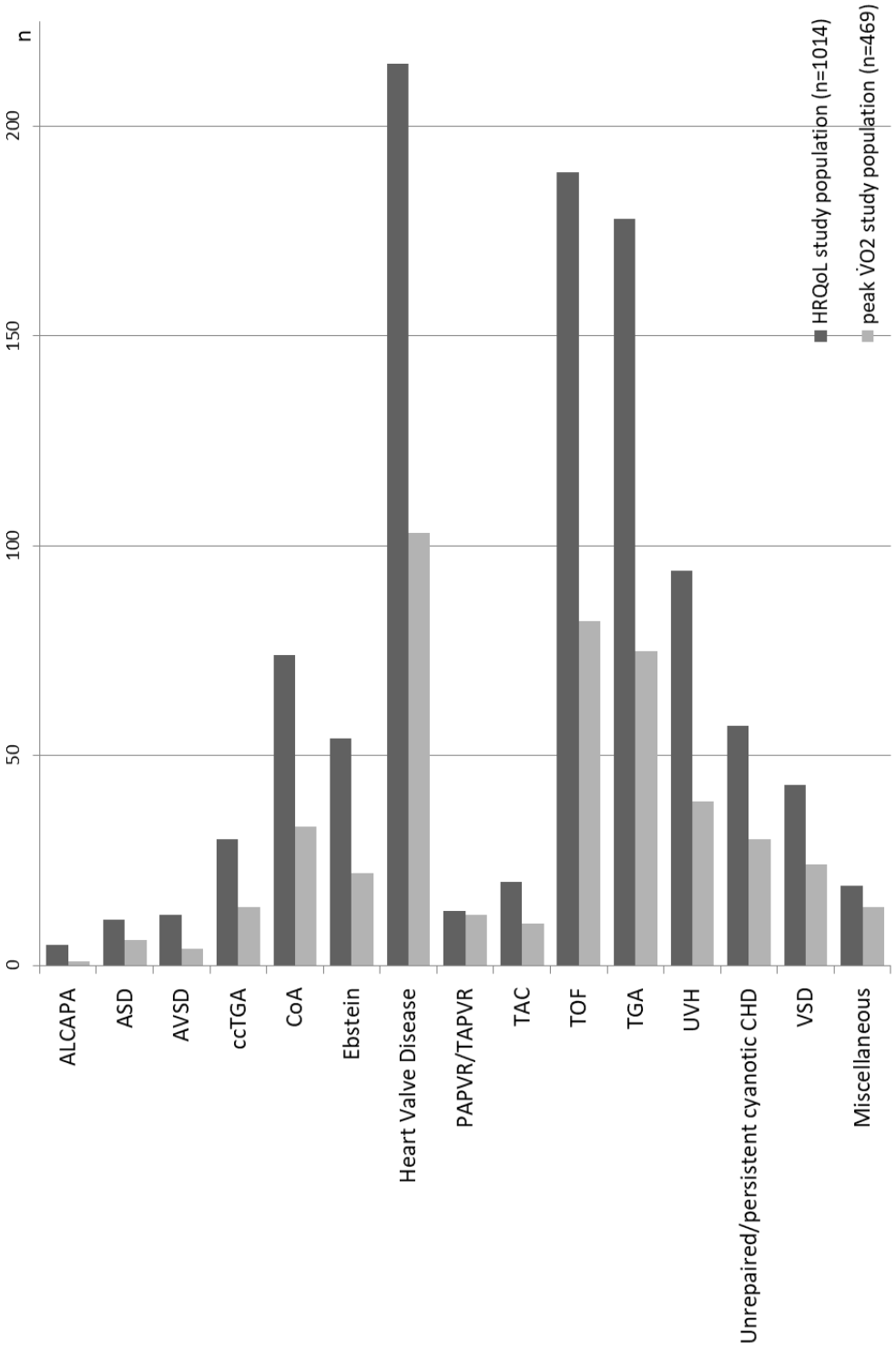
**Table 10: Diagnostic groups in the study population**

| *n (%)* | **HRQoL study population*** | **Peak $\dot{V}O_2$ study population*** |
|---|---|---|
| Total | 1014 | 469 |
| ALCAPA syndrome | 5 (0.5) | 1 (0.2) |
| ASD | 11 (1.1) | 6 (1.3) |
| AVSD | 12 (1.2) | 4 (0.9) |
| ccTGA | 30 (3.0) | 14 (3.0) |
| CoA | 74 (7.3) | 33 (7.0) |
| Ebstein's anomaly | 54 (5.3) | 22 (4.7) |
| Heart Valve Disease | 215 (21.2) | 103 (22,0) |
| Aortic valve regurgitation | 17 (1.7) | 7 (1.5) |
| Aortic valve stenosis | 123 (12.1) | 61 (13.0) |
| Mitral valve regurgitation/ prolapse | 10 (1.0) | 5 (1.1) |
| Mitral valve stenosis | 3 (0.3) | 2 (0.4) |
| Pulmonary valve stenosis | 57 (5.6) | 26 (5.5) |
| Tricuspid valve stenosis/regurgitation | 5 (0.5) | 2 (0.4) |
| PAPVR/ TAPVR | 13 (1.3) | 12 (2.6) |
| TAC | 20 (2.0) | 10 (2.1) |
| TOF | 189 (18.6) | 82 (17.5) |
| TGA | 178 (17.6) | 75 (16.0) |
| UVH | 94 (9.3) | 39 (8.3) |
| Unrepaired and persistent cyanotic defects | 57 (5.6) | 30 (6.4) |
| VSD | 43 (4.2) | 24 (5.1) |
| Miscellaneous | 19 (1.9) | 14 (3.0) |

**Patients with a combination of more than one cardiac defect were assigned to the diagnostic group of highest severity.*

| | | | |
|---|---|---|---|
| *ALCAPA* | *Anomalous left coronary artery from the pulmonary artery-syndrome* | *TAC* | *Truncus arteriosus communis (common arterial trunk)* |
| *ASD* | *Atrial septal defect* | *TAPVR* | *Total anomalous pulmonary venous return* |
| *AVSD* | *Atrioventricular septal defect* | | |
| *ccTGA* | *Congenitally corrected transposition of the great arteries* | *TOF* | *Tetralogy of Fallot* |
| | | *TGA* | *Transposition of the great arteries* |
| *CoA* | *Coarctation of the aorta* | *UVH* | *Univentricular heart/ single ventricle* |
| *PAPVR* | *Partial anomalous pulmonary venous return* | *VSD* | *Ventricular septal defect* |

**Figure 6: Diagnostic groups in the study population**



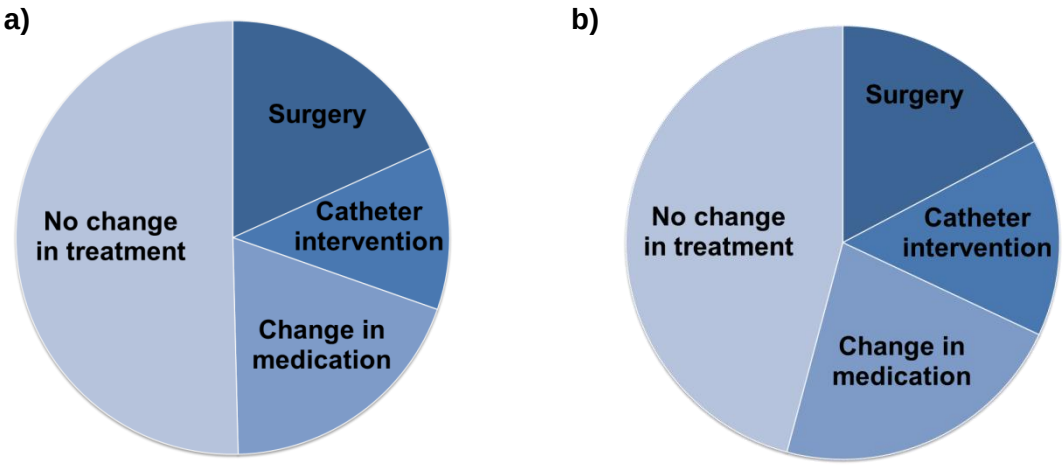

| | | | |
|---|---|---|---|
| *ALCAPA* | *Anomalous left coronary artery from the pulmonary artery-syndrome* | *TAC* | *Truncus arteriosus communis (common arterial trunk)* |
| *ASD* | *Atrial septal defect* | *TAPVR* | *Total anomalous pulmonary venous return* |
| *AVSD* | *Atrioventricular septal defect* | | |
| *ccTGA* | *Congenitally corrected transposition of the great arteries* | *TOF* | *Tetralogy of Fallot* |
| | | *TGA* | *Transposition of the great arteries* |
| *CoA* | *Coarctation of the aorta* | *UVH* | *Univentricular heart/ single ventricle* |
| *HRQoL* | *Health-related quality of life* | *VSD* | *Ventricular septal defect* |
| *PAPVR* | *Partial anomalous pulmonary venous return* | | |

Approximately half of the patients included did not receive any active treatment during follow-up, i.e. they were on surveillance with no changes in their treatment regimen. In the other half of patients who underwent some kind of treatment change between the baseline and follow-up examination, the largest treatment group was “change in medication”, followed by “heart surgery” and “catheter intervention”. (Table 11, Figure 7)

**Table 11: Treatment groups in the study population**

| **Treatment,** n (%) | **HRQoL study population (n=1014)** | **Peak $\dot{V}O_2$ study population (n=469)** |
|---|---|---|
| **Change in treatment** | 503 (49.6) | 254 (54.2) |
| Heart Surgery | 185 (18.2) | 81 (17.3) |
| Catheter Intervention | 123 (12.1) | 69 (14.7) |
| Change in Medication | 195 (19.2) | 104 (22.2) |
| **No change in treatment** | 511 (50.4) | 215 (45.8) |

**Figure 7: Treatment groups in a) the HRQoL study population and b) the peak $\dot{V}O_2$ study population**

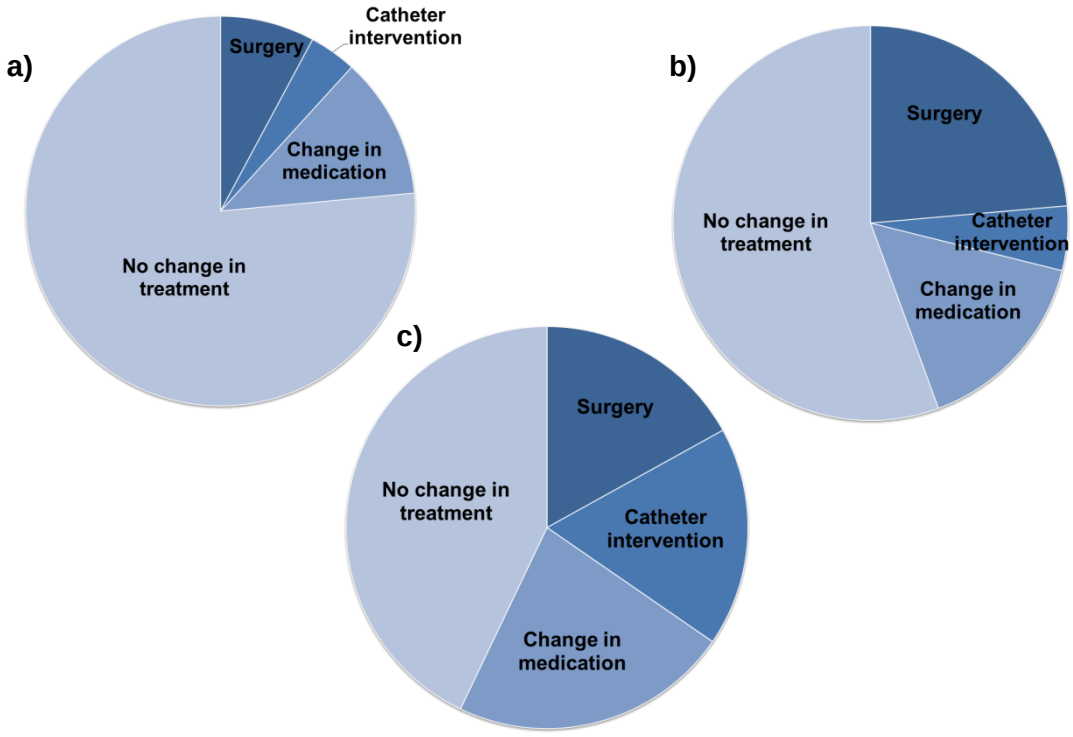


The distribution of the treatment groups varied between patients with different grades of severity. While the majority of patients with simple CHD did not receive any change in treatment during follow-up, the majority of patients with complex defects underwent some kind of treatment change. Patients with moderate defects underwent surgery more often compared to the other severity groups, while patients with complex defects had the highest rates of catheter intervention and change in medication compared to patients with less severe defects. (Table 12, Figure 8)

**Table 12: Treatment groups by severity grade**

| **Treatment,** n (%) | **Simple CHD (n=102)** | **Moderate CHD (n=322)** | **Complex CHD (n=578)** |
|---|---|---|---|
| **Change in treatment** | 24 (23.5) | 143 (44.4) | 330 (57.1) |
| Surgery | 8 (7.8) | 76 (23.6) | 98 (17.0) |
| Catheter intervention | 4 (3.9) | 17 (5.3) | 102 (17.6) |
| Change in medication | 12 (11.8) | 50 (15.5) | 130 (22.5) |
| **No change in treatment** | 78 (76.5) | 179 (55.6) | 248 (42.9) |

**Figure 8: Treatment groups in patients with a) simple, b) moderate, and c) complex CHD**



## 4.2 Overall changes in HRQoL and exercise capacity over time

In the total group of patients (n=1014), there were overall no significant changes in HRQoL over time. More specifically, the associated paired t-tests revealed t(1013)=-0.713, p=0.476 for changes in the physical summary score and t(1013)=0.706, p=0.480 for changes in the mental summary score. (Table 13)

Regarding exercise capacity (n=469), peak $\dot{V}O_2$ significantly deteriorated in total over time, with t(468)= -5.096, p<0.001 in the associated t-test. (Table 13)

**Table 13: Overall changes in HRQoL and exercise capacity over time**

| | Mean ± SD | p-value t-test[a] |
|---|---|---|
| **Physical summary score**[b] | | |
| Baseline | 51.83 ± 7.49 | |
| Follow-up | 51.67 ± 7.83 | |
| Change | -0.17 ± 7.38 | 0.476 |
| **Mental summary score**[b] | | |
| Baseline | 50.86 ± 8.78 | |
| Follow-up | 51.06 ± 8.60 | |
| Change | 0.20 ± 9.11 | 0.480 |
| **Peak $\dot{V}O_2$ (ml/kg/min)**[c] | | |
| Baseline | 28.58 ± 9.84 | |
| Follow-up | 27.38 ± 9.42 | |
| Change | -1.19 ± 5.07 | <0.001 |

*a) Paired t-test examining whether there were significant changes in the outcome variables over time*

*b) Measured in the total study population (n=1014)*

*c) Measured in the peak $\dot{V}O_2$ study population (n=469)*

## 4.3 HRQoL and exercise capacity according to diagnosis

At baseline, both HRQoL and peak $\dot{V}O_2$ differed significantly between the various diagnostic groups, with ANOVAs between the diagnostic groups reporting $F(25,988)=6.04$, $p<0.001$ for the baseline physical summary score of HRQoL, $F(25,988)=2.12$, $p=0.001$ for the baseline mental summary score of HRQoL and $F(25,443)=8.34$, $p<0.001$ for the baseline peak $\dot{V}O_2$.

On the contrary, no significant difference was detected between the various diagnostic groups with regard to changes of HRQoL and peak $\dot{V}O_2$ over time, with the values in the associated ANOVAs being $F(25,988)=0.68$, $p=0.881$ for changes in the physical summary score of HRQoL, $F(25,988)=1.23$, $p=0.206$ for changes in the mental summary score of HRQoL, and $F(25,443)=1.00$, $p=0.466$ for changes in peak $\dot{V}O_2$ over time.

## 4.4 HRQoL and exercise capacity according to severity grade

At baseline, both HRQoL and peak $\dot{V}O_2$ differed significantly between the severity groups. More specifically, the ANOVAs between the three severity groups were significant with $F(2,999)=21.44$, $p<0.001$ for the baseline physical summary score of HRQoL, $F(2,999)=7.22$, $p=0.001$ for the baseline mental summary score of HRQoL and $F(2,460)=54.68$, $p<0.001$ for the baseline peak $\dot{V}O_2$. Generally, higher complexity of the patient's defect was associated with worse HRQoL and reduced peak $\dot{V}O_2$ at baseline. (Table 14)

Changes in the physical summary score of HRQoL over time did not differ significantly between the severity groups, with the associated ANOVA reporting $F(2,999)=0.83$, $p=0.438$. ANOVA between the different severity grades yielded $F(2,999)=3.75$, $p=0.024$ for changes in the mental summary score and $F(2,460)=10.06$, $p<0.001$ for changes in peak $\dot{V}O_2$ over time. (Table 14)

**Table 14: HRQoL and peak V̇O2 according to severity grade**

| Mean ± SD | Simple | Moderate | Complex | p-value ANOVA[a] |
|---|---|---|---|---|
| **Physical summary score**[b] | | | | |
| Baseline | 55.24 ± 4.94 | 52.85 ± 6.62 | 50.65 ± 8.08 | <0.001 |
| Change over time | -0.18 ± 5.06 | -0.60 ± 7.30 | 0.06 ± 7.75 | 0.438 |
| **Mental summary score**[b] | | | | |
| Baseline | 52.35 ± 7.70 | 49.44 ± 9.46 | 51.49 ± 8.44 | 0.001 |
| Change over time | -0.08 ± 8.23 | 1.30 ± 9.55 | -0.42 ± 8.96 | 0.024 |
| **Peak $\dot{V}O_2$ (ml/kg/min)**[c] | | | | |
| Baseline | 38.14 ± 9.80 | 30.80 ± 9.10 | 25.44 ± 8.41 | <0.001 |
| Change over time | -3.81 ± 5.36 | -0.29 ± 5.48 | -1.16 ± 4.60 | <0.001 |

*a) ANOVA comparing the three severity groups*

*b) Measured in the total study population (n=1014)*

*c) Measured in the peak $\dot{V}O_2$ study population (n=469)*

*Note. Adapted from "Effects of Congenital Heart Disease Treatment on Quality of Life", by M. Boukovala, J. Müller, P. Ewert and A. Hager, 2019, The American Journal of Cardiology, 123(7), p. 1163-1168. Copyright 2019 by Elsevier Inc.*

## 4.5 HRQoL and exercise capacity according to treatment

### 4.5.1 "No change in treatment" vs. "change in treatment"

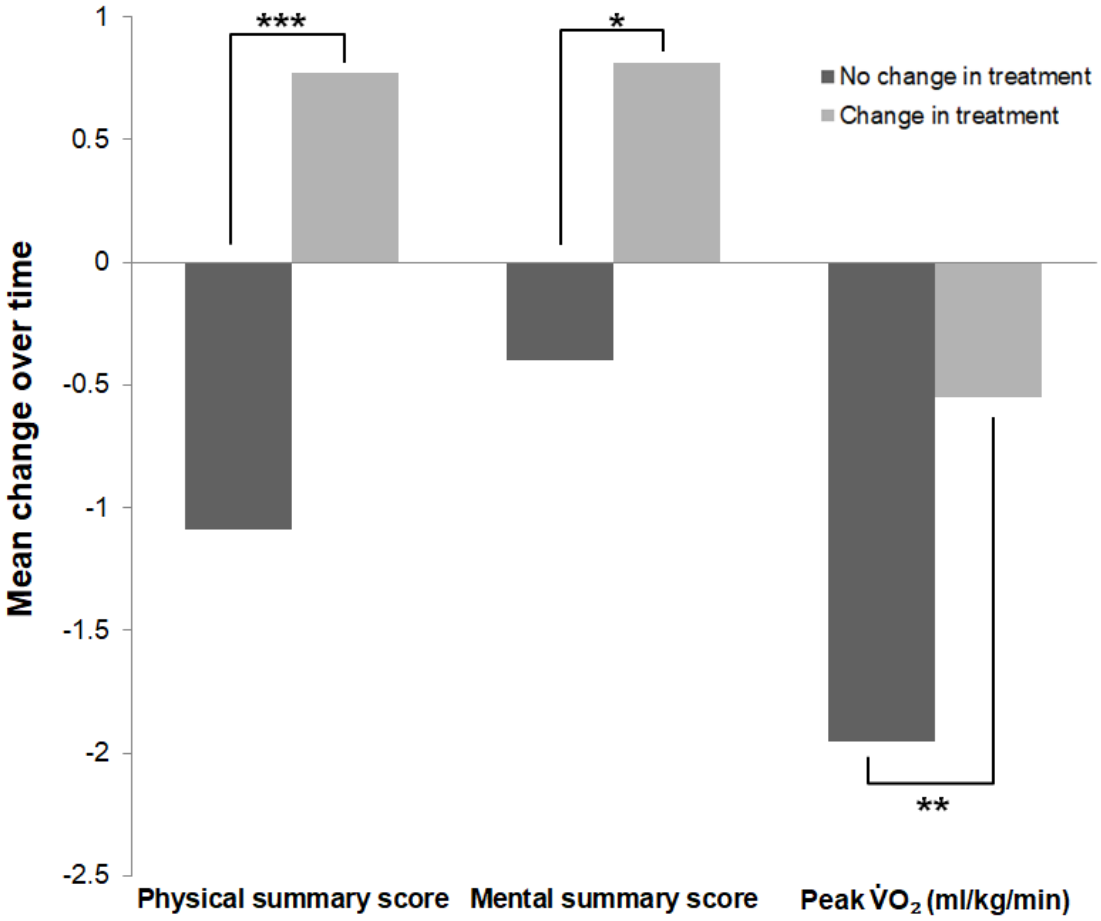
In general, patients who did not receive any change in treatment exhibited worse HRQoL and exercise capacity over time compared to those who received any kind of treatment during follow-up. More specifically, t-tests comparing the mean changes in HRQoL and exercise capacity over time between the groups "no change in treatment" and "change in treatment" (consisting of surgery, catheter intervention and change in medication) yielded significant differences, with t(972,148)=-4.03, p<0.001 for changes for the physical summary score of HRQoL, t(1012)=-2.13, p=0.034 for changes in the mental summary score of HRQoL, and t(389,008)=-2.93, p=0.004 for changes in peak $\dot{V}O_2$ over time. (Table 15, Figure 9)

**Table 15: Changes in HRQoL and peak V̇O2 in patients with "no change in treatment" vs. "change in treatment"**

| *Mean ± SD* | **No change in treatment** | **Change in treatment** | **p-value t-test *** |
|---|---|---|---|
| **Change in physical summary score** | -1.09 ± 6.61 | 0.77 ± 7.99 | <0.001 |
| **Change in mental summary score** | -0.40 ± 8.60 | 0.81 ± 9.58 | 0.034 |
| **Change in peak $\dot{V}O_2$ (ml/kg/min)** | -1.95 ± 5.78 | -0.55 ± 4.30 | 0.004 |

** T-test comparing the groups "no change in treatment" and "change in treatment"*

**Figure 9: Changes in HRQoL and peak V̇O2 in patients with "no change in treatment" vs. "change in treatment"**

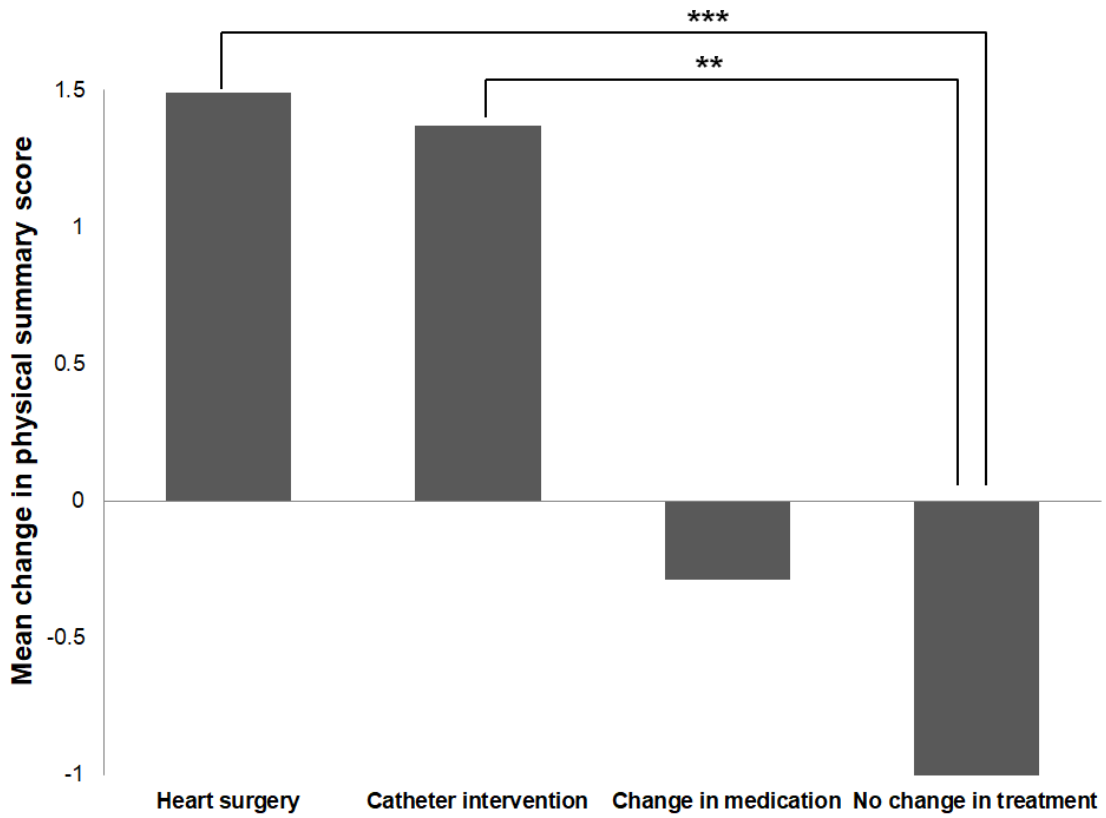


### 4.5.2 Comparison of the four treatment groups

**Physical summary score of HRQoL**

Changes in the physical summary score differed significantly between the four treatment groups, with $F(3,1010)=7.70$, $p<0.001$ in the associated ANOVA. Post hoc analysis demonstrated that patients with surgery and catheter intervention experienced significantly improved physical summary score compared to patients who received no change in treatment (Bonferroni $p<0.001$ and $p=0.005$, respectively) (Figure 10)

**Figure 10: Changes in the physical summary score of HRQoL in the four treatment groups**

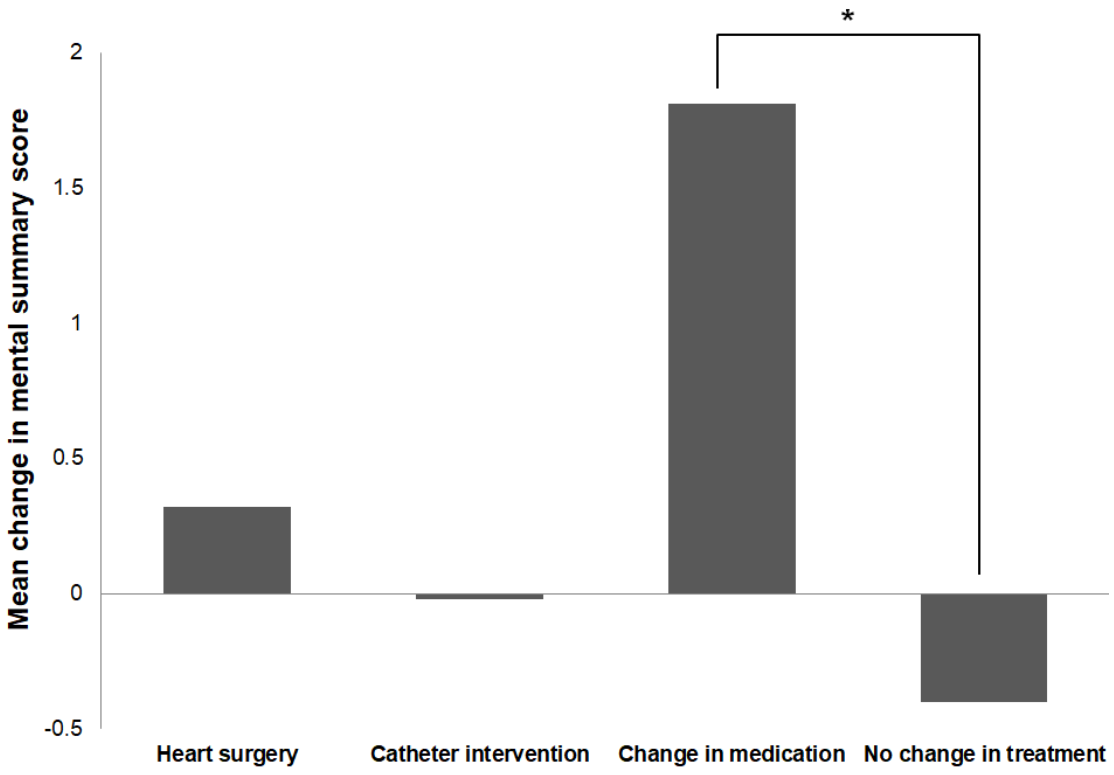


This effect remained significant in the multivariable regression analysis performed to assess the ability of the treatment options as well as further independent variables to predict changes in the physical summary score of HRQoL (see section 3.4.3 for a list of all independent variables included in the model). The results of the regression analysis indicated that four independent variables explained 24% of the physical summary score variance (adjusted $R^2$=0.24, F(4,1009)=79.97, p=<0.001). Surgery and catheter intervention were found to be significant predictors of improvement in physical HRQoL (Beta=0.06, p=0.026 and Beta=0.07, p=0.011, respectively), whereas the baseline values of the physical summary score (Beta=-0.48, p<0.001) and the age of the patients (Beta=-0.19, p<0.001) were found to be significant predictors of worsening.

**Mental summary score of HRQoL**

Changes in the mental summary score of HRQOL also differed significantly between the treatment groups, with F(3,1010)=2.82, p=0.038 in the associated ANOVA. More specifically, patients with change in their medication regimen exhibited improved mental HRQoL over time as compared to patients with no change in treatment (Bonferroni post hoc analysis p=0.024). (Figure 11)

**Figure 11: Changes in the mental summary score of HRQoL in the four treatment groups**

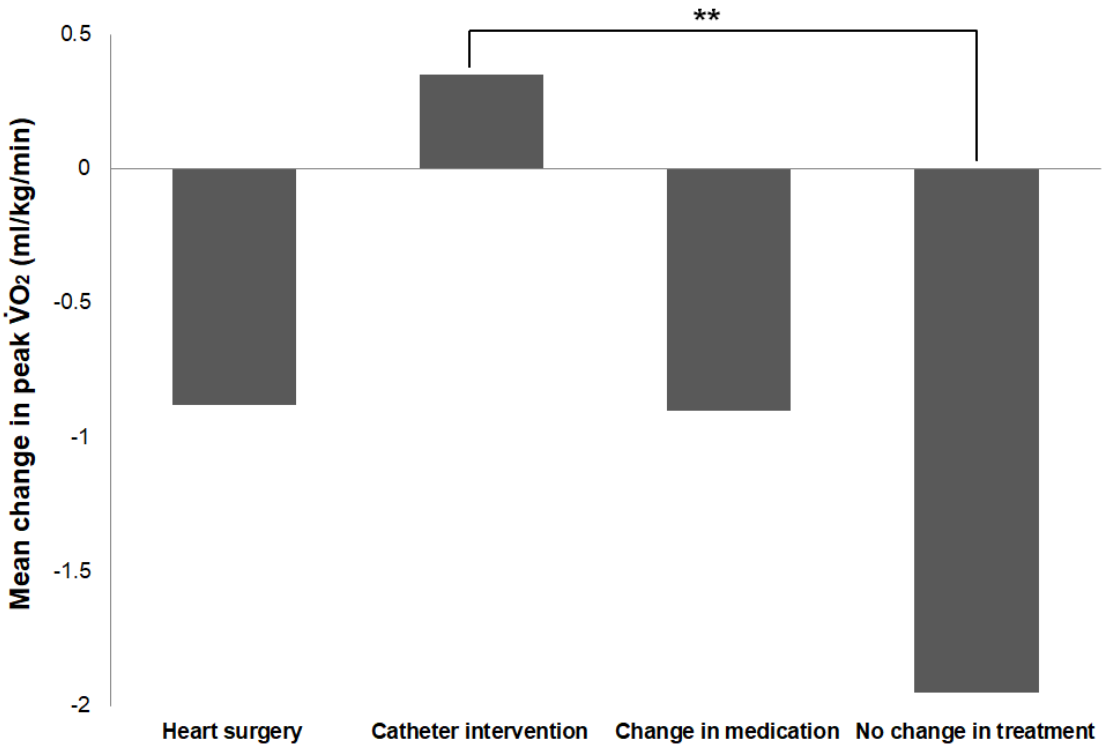


Nevertheless, this effect was not significant in the multivariable model including the treatment options along with other independent variables (see section 3.4.3 for a list of all independent variables included in the model). Results of the multiple regression analysis indicated that two independent variables explained 29% on the variation in the mental summary score of HRQoL (adjusted $R^2$=0.29, F(2,1011)=209.02, p<0.001). More specifically, the mental summary score at baseline and female sex were found to be significant predictors of worsening in mental HRQoL over time (Beta= -0.54, p<0.001 and Beta= -0.06, p=0.038, respectively). None of the treatment options, including change in medication, demonstrated the ability to predict changes in mental HRQoL in this analysis.

**Exercise capacity**

Significant differences were detected between the four treatment groups regarding changes of peak $\dot{V}O_2$ over time, with F(3,465)=4.02, p=0.008 in the associated ANOVA. Post hoc testing indicated that patients who received catheter intervention showed significant improvement of their exercise capacity compared to patients who received no change in treatment (Bonferroni post hoc analysis p=0.006). (Figure 12)

**Figure 12: Changes in peak $\dot{V}O_2$ in the four treatment groups**



However, this effect was not evident in the associated multivariable regression analysis (see section 3.4.3 for a list of all independent variables included in the model). Results of the multiple regression analysis indicated that five predictors explained 20% of the variation of changes in peak $\dot{V}O_2$ over time (adjusted $R^2$=0.20, F(5,463)=24.907, p<0.001). The five variables identified as significant predictors of worsening of exercise capacity were the baseline values of peak $\dot{V}O_2$ (Beta= -0.45, p<0.001), presence of a pacer/ICD (Beta= -0.14, p=0.001), duration of follow-up (Beta=-0.17, p<0.001), BMI (Beta=-0.24, p<0.001), and female sex (Beta=-0.10, p=0.036). None of the treatment options, including catheter intervention, were identified as significant predictors.

Following table summarizes the results regarding changes in HRQoL and exercise capacity in the four treatment groups. (Table 16)

**Table 16: HRQoL and exercise capacity according to treatment**

| | Heart surgery | Catheter intervention | Change in medication | No change in treatment | p-value ANOVA[a] |
|---|---|---|---|---|---|
| **Physical summary score** | | | | | |
| Baseline | 49.65±8.55 | 50.90±7.57 | 49.05±8.95 | 53.91±5.63 | |
| Follow-up | 51.14±7.64 | 52.27±7.04 | 48.76±9.28 | 52.82±7.17 | |
| Change | 1.49±8.76* | 1.37±6.49* | -0.29±8.01 | -1.09±6.61 | <0.001[b] |
| **Mental summary score** | | | | | |
| Baseline | 49.87±8.74 | 50.89±8.43 | 48.79±10.36 | 51.99±8.03 | |
| Follow-up | 50.19±8.28 | 50.87±9.01 | 50.60±9.09 | 51.59±8.41 | |
| Change | 0.32±9.79 | -0.02±9.51 | 1.81±9.38 | -0.40±8.60 | 0.038[c] |
| **Peak $\dot{V}O_2$ (ml/kg/min)** | | | | | |
| Baseline | 25.21±8.20 | 26.33±7.41 | 24.25±8.49 | 32.66±10.14 | |
| Follow-up | 24.34±8.07 | 26.68±8.41 | 23.35±8.44 | 30.71±9.51 | |
| Change | -0.88±4.49 | 0.35±4.01 | -0.90±4.28 | -1.95±5.78 | 0.008[d] |

*a) ANOVA comparing the four treatment groups*

*b) Significant difference between "heart surgery" and "no change in treatment" (p<0.001) as well as "catheter intervention" and "no change in treatment" (p=0.005) in Bonferroni post hoc testing (underlined)*

*c) Significant difference between "change in medication" and "no change in treatment" (p=0.024) in Bonferroni post hoc testing (underlined)*

*d) Significant difference between "catheter intervention" and "no change in treatment" (p=0.006) in Bonferroni post hoc testing (underlined)*

** Still significantly better after including also age, sex, body mass, body height, body mass index, baseline values of the outcome variable and follow up duration in a multivariable regression model*

*Note. Adapted from "Effects of Congenital Heart Disease Treatment on Quality of Life", by M. Boukovala, J. Müller, P. Ewert and A. Hager, 2019, The American Journal of Cardiology, 123(7), p. 1163-1168. Copyright 2019 by Elsevier Inc.*

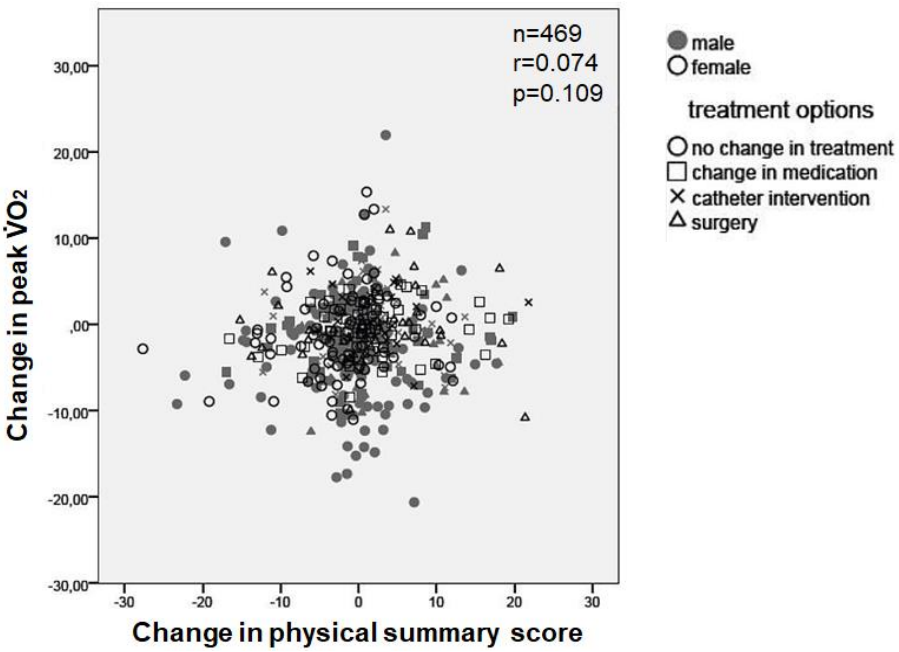
## 4.6 Correlation between longitudinal HRQoL and exercise capacity

In this analysis, changes in HRQoL did not correlate with changes in exercise capacity over time. More specifically, there was no correlation between changes in the physical summary score of HRQoL and changes in peak $\dot{V}O_2$ over time (r=0.074, p=0.109). The same applies to the correlation between changes in the mental summary score of HRQoL and those in peak $\dot{V}O_2$ (r=0.027, p=0.561). (Figure 13)

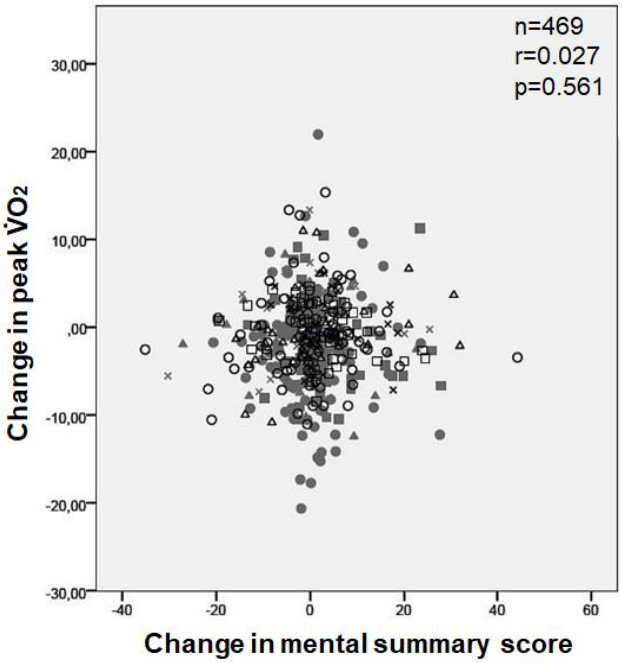
**Figure 13: Correlation between changes in peak V̇O2 and changes in a) the physical summary score and b) the mental summary score of HRQoL**

*Adapted from "Effects of Congenital Heart Disease Treatment on Quality of Life", by M. Boukovala, J. Müller, P. Ewert and A. Hager, 2019, The American Journal of Cardiology, 123(7), p. 1163-1168. Copyright 2019 by Elsevier Inc.*

**a)**




**b)**



# 5 Discussion

This study demonstrated that surveillance alone was associated with poorer HRQoL over time as compared to active treatment. Regarding the specific interventions, adolescents and adults with CHD rated their physical HRQoL better after surgery and catheter intervention compared to the other treatment options, despite this effect not being apparent in the objectively measured exercise capacity estimated by the peak $\dot{V}O_2$ during CPET.

Adolescents and adults with CHD are a very heterogeneous patient group**,** characterized by a remarkable variety of diagnoses and a wide spectrum of severity grades. In our analysis, we found that baseline HRQoL differed significantly between the various diagnostic groups and grades of severity. This is consistent with existing literature including the review studies of Fteropouli et al. (Fteropoulli et al., 2013) and Kahr et al. (Kahr et al., 2015) which suggest that more complex conditions are associated with poorer quality of life, especially with regard to its physical components. However, since this was a longitudinal study, we were mainly interested in changes of the outcome variables over time. Our findings indicate that changes in HRQoL over time, at least with regard to its physical components, did not differ significantly between diagnostic groups and severity grades. Therefore, we did not divide the study population into subgroups based on their condition, but considered all patients to be one combined cohort with the common general characteristic of CHD. Although this approach does not allow the evaluation of specific interventions or drugs, it can serve as a more comprehensive orientation framework, regardless of the specific underlying condition.

In this study, neither physical nor mental HRQoL showed significant changes over time in the overall study population. Taking into consideration that literature on the relationship between age and HRQoL in patients with CHD is partly inconclusive, our results might be supportive of reports demonstrating no association between age and HRQoL in this patient population (Teixeira et al., 2011). Nevertheless, it could be argued that the follow-up duration of 4.0 ± 2.2 years is too short to allow any conclusions regarding associations with age. Possibly, changes in HRQoL may have been evident with longer follow-up duration. On the contrary, exercise capacity slowly deteriorated over time in the overall study population, in line with previously published results of Müller et al. from a longitudinal study including patients who underwent no change in treatment between the baseline and follow-up examinations (Muller, Ewert, & Hager, 2015). Although the follow-up duration in the subgroup of patients evaluated for changes in peak $\dot{V}O_2$ in this study was short (2.8±1.3 years), this observation is

consistent with available literature indicating that exercise capacity declines with advancing age (Diller et al., 2005; Muller et al., 2014a).

## 5.1 Treatment effectiveness

Approximately half of the patients included in this study were on surveillance without any active therapeutic intervention between the baseline and follow-up examination (”no change in treatment” group), while the other half received some kind of active treatment, including heart surgery, catheter intervention or change in medication (“change in treatment” group). In our analysis, active treatment was associated with improved outcome compared to surveillance across all investigated outcome variables. Although the absolute changes over time were small, both physical and mental HRQoL improved in patients who received active treatment, while patients on surveillance experienced a deterioration of HRQoL over time. Regarding the objectively measured exercise capacity, both treatment groups experienced decline over time; however, this decline was more pronounced in patients on surveillance compared to patients who received active treatment.

In order to evaluate the specific treatment options individually, we looked at all different types of interventions patients received between the baseline and follow up examination and analyzed the outcome variables by the four main treatment groups, i.e. surgery, catheter intervention, change in medication, and no change in treatment. We found that surgery and catheter intervention were associated with significant improvement in physical HRQoL compared to the other treatment options, with this finding being confirmed in a multivariable model accounting for additional potential predictors. Of note, the physical summary score of the SF-36 includes the aspects of physical functioning, physical role, bodily pain and general health perception from the patient’s point of view. This finding is partly supportive of our initial hypothesis and is consistent with the results of follow-up studies focusing on specific surgical and/or interventional procedures for specific CHD. For instance, Mohr et al. showed in a large-scale longitudinal study that the majority of the patients reported improvement of their self-perceived general health condition following surgical or transcatheter aortic valve replacement (Mohr et al., 2014). Moreover, Müller et al. demonstrated that percutaneous pulmonary valve implantation lead to significant improvement mostly in the physical domains of HRQoL (Muller et al., 2014b). Cross-sectional studies in patients with CHD after heart surgery deliver conflicting results. While several studies report very good QoL compared to the standard population (Heusch et al., 2014; Loup et al., 2009; Muller et al., 2009), others report poor QoL following open heart surgery

(Landolt, Valsangiacomo Buechel, & Latal, 2008; Latal et al., 2009; Spijkerboer et al., 2006; Tahirovic, Begic, Tahirovic, & Varni, 2011). However, these studies are cross-sectional and compare CHD patients with healthy references. Therefore, they do not allow us to draw any solid conclusions regarding the actual effects of the investigated procedures on longitudinal HRQoL. This underlines the imperative need for large-scale longitudinal studies evaluating specific surgical and interventional procedures in terms of patient-reported outcomes.

In our analysis, the comparison between the four treatment groups also revealed an association of change in medication with better mental HRQoL over time as well as catheter intervention with improved exercise capacity. Nevertheless, these observations were not confirmed in the multivariable model which included additional variables as potential predictors. More studies, ideally prospective, are necessary to further explore these associations.

## 5.2 Predictors of longitudinal HRQoL and exercise capacity

Apart from the treatment options, the performed multivariable regression analysis investigated the role of additional independent variables as predictors of outcome, providing us with a better insight into the factors that influence HRQoL and exercise capacity in adolescents and adults with CHD.

In our analysis, we found female sex to be a negative predictor of longitudinal changes in mental HRQoL and exercise capacity. Although some authors report no association between sex and HRQoL in patients with CHD (Silva et al., 2011; Teixeira et al., 2011), our finding is consistent with existing literature suggesting that female sex is associated with poor HRQoL, mainly with regard to its mental components (Amedro et al., 2016a; Muller et al., 2017a; Vigl et al., 2011). Regarding exercise tolerance, reduced values have been associated with female sex in existing studies (Kempny et al., 2012; Kuehl et al., 2015). It is noteworthy that a difference between the two sexes is evident also in healthy individuals, with healthy men generally exhibiting higher peak $\dot{V}O_2$ compared to healthy women mainly due to peripheral factors including higher muscle mass and hemoglobin concentration (Kempny et al., 2012). Women, including those with CHD, have been reported to be less physically active, which may also contribute to a more pronounced decline in exercise capacity over time in women (Muller et al., 2017a; Muller et al., 2012a). Interestingly, Kempny et al. did not detect any difference in exercise capacity between male and female patients with Eisenmenger syndrome in contrast to patients with less complex physiology, indicating that

cardiac limitations likely predominate peripheral factors in patients with complex cardiac defects (Kempny et al., 2012).

In line with previously published results (Kuehl et al., 2015), we also found that higher BMI was a negative predictor of exercise capacity in the multivariable model. Interestingly, Brida et al. reported that higher BMI was associated with lower mortality independently from peak $\dot{V}O_2$ (Brida et al., 2017). This was especially pronounced in symptomatic patients with complex CHD, possibly driven by the detrimental effects of cardiac cachexia. Based on these results, Brida et al. suggest that mildly overweight patients with preserved exercise capacity may have the best prognosis amongst adults with CHD (Brida et al., 2017).

Our multivariable regression analysis identified the presence of pacemaker to be predictive of decline in exercise capacity. This finding is consistent with previous studies reporting an association between presence of a pacemaker and impaired exercise capacity (Muller et al., 2017a; Muller et al., 2015). Of note, the presence of cardiac devices has also been consistently shown to be associated with impaired QoL (Czosek et al., 2012; Gutierrez-Colina et al., 2014; Muller et al., 2017a).

## 5.3 Association between longitudinal HRQoL and exercise capacity

One of the secondary objectives of our study was to assess the relationship between longitudinal patient-reported HRQoL and objectively measured exercise capacity. We found that changes in peak $\dot{V}O_2$ did not correlate with changes in the physical as well as mental summary scores of HRQoL over time, a finding consistent with previously published results by Ehlert et al. based on a smaller cohort of 182 patients. Ehlert et al. demonstrated that patients with CHD did report changes in their objectively measured exercise capacity as corresponding changes in subjective HRQoL (Ehlert et al., 2012). In other words, patient-reported HRQoL in this patient population seems to be independent from improvement or deterioration of exercise capacity. This is possibly explained by life-long adaptation of these chronically ill patients to their exercise-related limitations (Mantegazza et al., 2017). Since QoL is largely affected by individual experience and expectations (Carr, Gibson, & Robinson, 2001), patients with CHD likely consider exercise tolerance to be less influential for their overall well-being, while other factors such as social or emotional well-being are likely weighed as more important. As a result, it is possible that even if they experience a decline in exercise

capacity, they either do not recognize it or they do not consider it impairing enough to affect their overall well-being and life satisfaction (Ehlert et al., 2012).

In our study, patients reported improved physical HRQoL after heart surgery and catheter intervention, despite this effect not being apparent in the objectively measured exercise capacity. Interestingly, this suggests that adolescents and adults with CHD may perceive more “active” forms of treatment as overall more beneficial, even if they do not result in a measurable improvement of their cardio-pulmo-vascular functioning. This finding may be partly explained by the patients’ expectations regarding the outcome of these procedures, as expectations are considered to play a significant role in shaping an individual’s experience and behavior according to the response expectancies theory in psychology (Kirsch, 1985).

Taken together, it is evident that HRQoL and exercise capacity provide complementary information about a patient’s functional health; hence, they should be considered concurrently in the evaluation of adolescents and adults with CHD.

## 5.4 Limitations

In this study, HRQoL was assessed with the SF-36 survey, which is a generic instrument that can be used regardless of age, disease and treatment group (Aaronson et al., 1992). Unlike disease-specific instruments, the SF-36 does not focus on disease-specific symptoms, but evaluates the overall influence of symptoms and limitations on subjective health and well-being. However, it may be too imprecise to detect minute changes in HRQoL over time. At the same time, some may argue that the SF-36, especially the physical domains including the physical summary score, represents more a self-reported health status. Mainly the domain “mental health” is considered to depict more accurately “real” quality of life. In a study, it is essential to weigh the advantages of depicting “real” quality of life, where small treatment-specific changes often remain undetected, against the precision of a disease-specific PRO instrument. In this study, we included a fairly large cohort of patients (n=1014), so that clinically relevant fluctuations should have been clearly detected.

The Department of Pediatric Cardiology and Congenital Heart Defects of the German Heart Centre Munich ("Deutsches Herzzentrum München") is a tertiary referral center for patients with CHD of any age. Therefore, patients seen in the outpatient clinic of our institution often have more complex CHD compared to the general CHD population, with a ratio of 1:3:5 for simple: moderate: complex defects (Table 9). Of note, the medical care of patients with more complex defects is especially challenging in the

cohort of adolescents and adults with CHD. Nevertheless, this referral bias with over-representation of patients with severe defects needs to be taken into consideration when extrapolating results from this study to the general population of patients with CHD. A referral bias based on the indication for CPET can be ruled out, as this examination is part of the routine monitoring of patients in the tertiary department of our institution, with only a few individual cases undergoing CPET due to a specific indication such as new symptoms. Since patients not surviving to a follow-up examination and patients with a major neurological deficit incapable of completing the SF-36 survey were excluded from the study, sampling bias towards a healthier patient cohort cannot be ruled out.

Furthermore, this study was not designed to evaluate a specific drug or procedure but the main treatment options, i.e. heart surgery, catheter intervention, change in medication and surveillance, as combined treatment groups. Since this was not a randomized trial, it is possible that the patients' underlying condition may have determined the received treatment by indication to a great extent. Suggestive of this limitation is the distribution of the four treatment options in the different severity groups (Table 12, Figure 8). For instance, while patients with simple CHD were most likely to remain on surveillance (76.5%), the majority of patients with complex CHD received some kind of intervention (57.1%), with the most common being change in medication (22.5%) followed by heart surgery (17%). However, this limitation holds true for all four investigated treatment groups.

Lastly, the follow-up time in the total study population was noticeably longer than in the subgroup included in peak $\dot{V}O_2$ analysis (4.0±2.2 vs. 2.8±1.3 years). This needs to be taken into consideration when interpreting results regarding changes in HRQoL and peak $\dot{V}O_2$.

## 5.5 Future research

The growing population of adolescents and adults with CHD, which is characterized by low mortality but substantial morbidity, differs substantially from children with CHD with regard to cardiac defect pathophysiology, co-morbidities as well as cognitive and emotional functioning. Hence, findings of treatment studies conducted in children can only be applied in the adult patient population by extrapolation. This has created an imperative need for treatment studies that focus exclusively in the grown-up population with CHD and evaluate interventions longitudinally in terms of functional health variables, including HRQoL. Despite its longitudinal design, this was a retrospective study and as such, the interpretation of its results is subject to limitations due to

common potential sources of error such as confounding and bias. Although it may have provided us with valuable hypothesis-generating results, these need to be tested prospectively in future studies. In our analysis, we did not detect significant differences between the diagnostic or severity groups regarding the changes of HRQoL over time; however, stratification by baseline condition either in form of combined diagnostic groups or grade of severity might be useful, since the underlying condition and its severity often determine treatment selection by indication. For the evaluation of HRQoL in future studies, a combination of the generic SF-36 survey with disease-specific instruments might prove beneficial, as it would possibly facilitate a more accurate assessment of subtle changes in HRQoL not detectable by the SF-36 alone.

# 6 Summary

The diagnostic and therapeutic advancements of the last decades have led to an expanding population of adolescents and adults with CHD, which is characterized by an overall low mortality but substantial morbidity. In these patients, functional health variables such as HRQoL and exercise capacity have become a key measure for the evaluation of health-care outcomes. The effectiveness of the various treatment options in terms of changes in functional health in this patient population remains largely unclear. In this retrospective, longitudinal study on a fairly large cohort of adolescents and adults with CHD, we found that active treatment was generally associated with better HRQoL over time as compared to surveillance alone. Adolescents and adults with CHD reported better physical HRQoL after surgery and catheter intervention, despite this effect not being apparent in the objectively measured exercise capacity estimated by the peak $\dot{V}O_2$ during CPET. No association was found between changes in HRQoL and changes in exercise capacity over time. Hence, parallel assessment of patient-reported HRQoL and objectively measured outcome such as exercise capacity is essential in the evaluation of adolescents and adults with CHD. This holds also true for the assessment of health-care outcomes in both cross-sectional and longitudinal treatment studies in this patient population.

**NOTE:**

- Parts of this work were published under the title "Effects of Congenital Heart Disease Treatment on Quality of Life" in the American Journal of Cardiology (2019).

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- Aspects of this work were presented orally in the annual conference of the German Association for Pediatric Cardiology in Leipzig, Germany (2017).

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