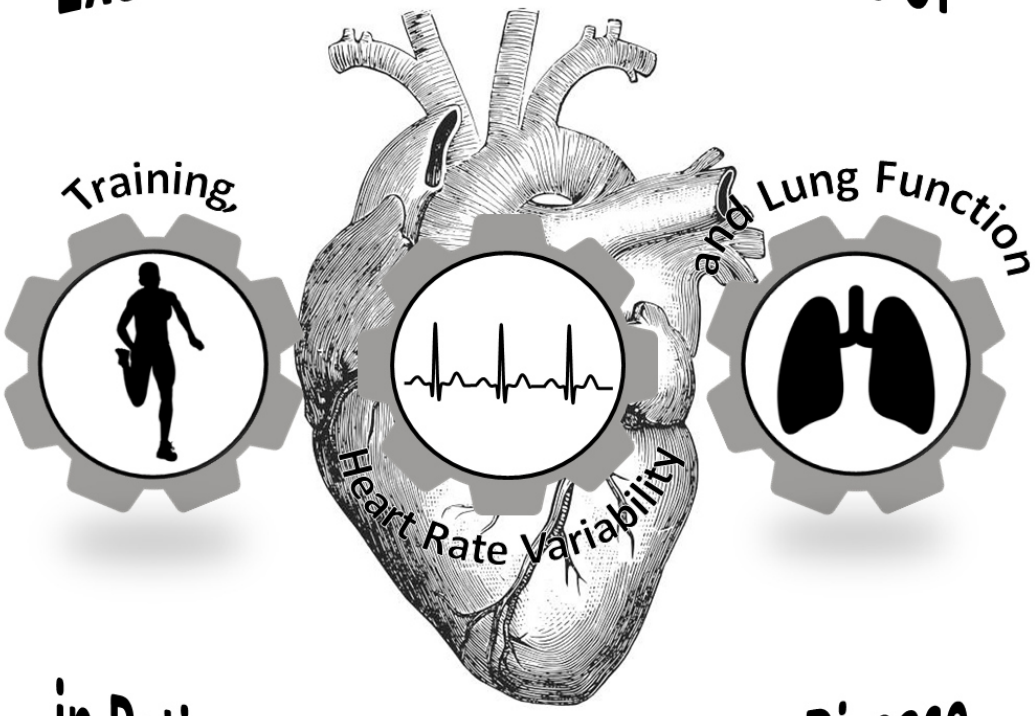
Exercise Capacity in the Context of



in Patients with Congenital Heart Disease

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Exercise Capacity in the Context of Training, Heart Rate Variability and Lung Function in Patients with Congenital Heart Disease

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List of Abbreviations

ACHD	Adults with Congenital Heart Disease
ANS	Autonomic Nervous System
APA	Atriopulmonary Anastomosis
AS	Aortic Stenosis
ASD	Atrial Septal Defect
AVA	Atrioventricular Anastomosis
AVSD	Atrioventricular Septal Defect
cAVSD	Complete Atrioventricular Septal Defect
ccTGA	Congenitally Corrected Transposition of the Great Arteries
CG	Control Group
CHD	Congenital Heart Disease
CoA	Coarctation of the Aorta
CO_2	Carbon Dioxide
CPET	Cardiopulmonary Exercise Test
CPX	Cardiopulmonary Exercise Test
DILV	Double-Inlet Left Ventricle
DIRV	Double-Inlet Right Ventricle
DORV	Double-Outlet Right Ventricle
FEV_1	Forced Expiratory Volume in the first second
FVC	Forced Vital Capacity
HIIT	High Intensity Interval Training
HIT	High Intensity Training
HRV	Heart Rate Variability
IG	Intervention Group
IMT	Inspiratory Muscle Training
LHO	Left Heart Obstruction
lnRMSSD	natural logarithm of Root Mean Square of Successive Differences
MD	Mean Differences
NN	Normal-to-Normal interval

O_2	Oxygen
pAVSD	Partial Atrioventricular Septal Defect
PCPC	Partial Cavopulmonary Connection
PDA	Patent Ductus Arteriosus
PS	Pulmonary Stenosis
RER	Respiratory Exchange Ratio
RHO	Right Heart Obstruction
RMSSD	Root Mean Square of Successive Differences
SDNN	Standard Deviation of all Normal-to-Normal Intervals
SI	Stress Index
SpO_2	Peripheral capillary Oxygen Saturation
TCPC	Total Cavopulmonary Connection
TGA	Transposition of the Great Arteries
ToF	Tetralogy of Fallot
UVH	Univentricular Heart
$\dot{V}O_2peak$	Peak Oxygen Uptake
VSD	Ventricular Septal Defect

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1 Introduction

Congenital heart defects (CHD) are the most common form of birth defects.[1] They represent the most frequent single organ malformations in humans, implicating structural anomalies of the heart or intrathoracic great vessels which is actually or potentially of functional significance.[2, 3] The manifestations result in various pathomorphological modifications including a large variety of symptoms.[4] According to the type of heart disease, some simple forms do not even require cardiologic care, while in complex forms of CHD interventional and surgical procedures and a lifelong need for medical care are inevitable, or these forms are even incompatible to life.[4, 5]

The prevalence of cardiac malformations within the years 2000-2005 is approximately 8 per 1000 live births in Europe.[6] From 1985 to 2000 the prevalence of children with severe CHD increased by 22%, in adults with severe CHD even by 85%.[1] In the past, CHD was considered a predominantly pediatric condition and only patients with simple CHD survived.[1] Nowadays, 90% of children with CHD reach adulthood and the majority of CHD population consists of adults, since the prevalence and the median age, especially of patients with more complex CHD, increased.[1, 4, 7] Mortality rates in patients with CHD have shifted away from the infant and childhood period towards adulthood, with a steady rise in the age of death.[8] Factors contributing to decreased mortality may include improvements in prevention, diagnostics, surgical and interventional procedures, outpatient management, medical care, and understanding of cardiovascular conditions in recent decades.[7, 9-11] Due to improved survival the CHD population, especially patients with severe CHD, will change towards more complex and longer living CHD patterns over the next few decades (Figure 1).[12]

While patients with the simplest forms of CHD do not require special aftercare, patients with complex, moderate and partly simple CHD need to be seen regularly in adult CHD (ACHD) centers. The majority of the adult patients is exposed to a medium to high risk of more diverse and numerous late complications leading to premature death, why long-term medical aftercare is crucial in this population.[7, 12] These patients are prone to the development of cardiac problems and additional acquisition of life-long comorbid conditions such as endocarditis, coronary artery disease, arrhythmia, pulmonary arterial hypertension and even heart failure.[8, 12] Re-operations and specialist interventions as well as intensive follow-ups are essential prerequisites for cardiac and medical care, improving health status.[7, 11, 12] Additionally, health care providers and patients will have to deal with different cardiac and hemodynamic problems from those currently seen.[12] With such a changing CHD population it is crucial to

ensure the patients continued health which requires education of both health care providers and patients, sharing responsibility of their life and care.[13]

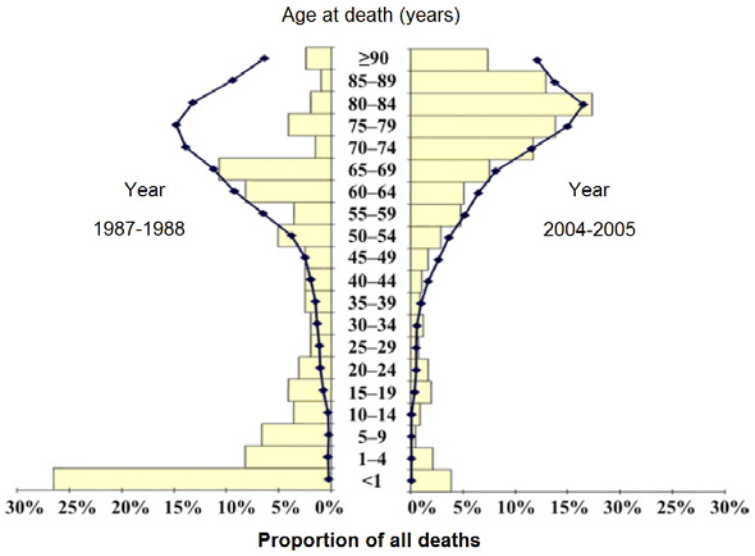

Figure 1: Distribution of age at death in patients with congenital heart disease in 1987 to 1988 and 2004 to 2005
Histogram bars depict the proportion of all deaths (x-axis) according to age at death (y-axis) in the cohort of patients with congenital heart disease in the first (1987 to 1988; left) and final (2004 to 2005; right) years of observation. Bold black curves with diamonds represent the corresponding age at death distribution in the general Quebec population during the same periods of observation. Modified from[8]

In the past, due to fear of possible sequels, prohibitions concerning physical activity were predominantly imposed and permissions given only reluctantly.[14, 15] As the risk of sudden cardiac death in patients with CHD is not reduced by activity restrictions, recommendations and guidelines regarding physical activities and sedentary behavior, were published in recent years.[16-20] There is agreement on the importance of an active lifestyle and regular physical activity resulting in several physiological, psychosocial and functional benefits on various health outcomes, including prevention of cardiovascular disease and all-cause mortality.[21] Nevertheless, physical inactivity remains one of the biggest problems not only in patient populations but society in general.[22] In comparison to the general population most patients with CHD have a more sedentary lifestyle and do not participate in regular exercise programs.[23, 24] These facts are of concern, since patients with CHD have in any case an increased risk of developing diabetes, obesity, hypertension, atherosclerotic cardiovascular disease, exercise intolerance and psychosocial morbidities.[8, 12, 24]

Physical inactivity does not only increase the probability of developing morbidities, it also results in a decreased exercise capacity, which is the strongest predictor of mortality and morbidity in patients with CHD.[21, 25-28] In comparison to the general population, patients with CHD show reduced exercise capacity.[19, 29, 30] Since an improvement of objective and

subjective exercise capacity is resulting in a decreased risk for hospitalization or death as well as in an increased health outcome and survival, physical exercise training has become an essential part of the CHD management.[19, 30-33] In order to make a safe recommendation on physically active lifestyles, sport eligibility testing is required to identify residuals with a specific risk for adverse events during physical activity. Sport eligibility is determined by the patient's individual risk that acute cardiac problems may occur related to activity or develop in the long-term due to certain exercise. Only in rare and complex cases precautions have to be taken to minimize the risk of cardiac events. Most patients with CHD can integrate physical activity in their daily life, join regular sport clubs with no risks and increase their exercise performance and capacity.

An active lifestyle not only increases exercise capacity, but also improves the regulation of the autonomic nervous system (ANS).[28, 34] ANS contributes significantly to homeostasis by regulating among others blood pressure, heart rate and respiration and adapting them to continuously changing environmental conditions.[35] A limitation of the ANS is associated with cardiac electrical instability, resulting in arrhythmic complications and mortality.[36, 37] This fact is of concern, as the vast majority of patients with CHD suffer from broad limitations of the ANS.[38-41] In the general population it has been shown that a restricted regulation of the ANS could be improved by physical activity.[28, 34] The association of ANS and exercise capacity in patients with CHD is currently not clear, but a possible association would offer a potential therapeutic approach to reduce mortality and morbidity. Exercise capacity is not solely dependent on cardiovascular, but also on pulmonary factors.[42, 43] Respiratory muscle weakness in patients with CHD correlates well with reduced exercise capacity.[44, 45] Patients with severe CHD, especially patients with Fontan circulation, suffer from impaired lung function which contributes to a limitation of exercise performance.[39, 44] Nevertheless, an increase in respiratory muscle strength is associated with improved exercise capacity in patients with CHD.[46, 47]

Considering the entire CHD population, patients with complex severity show the most impaired exercise capacity, implicating different cardiac and hemodynamic problems, comorbid conditions, re-operations and further late complications.[7, 8, 11, 12, 43, 48] Patients with complex CHD would benefit mostly from an improvement in exercise capacity and therefore special attention needs to be paid to these patients in medical aftercare.

2 Study purpose

There is agreement on the importance of an active lifestyle and regular physical activity as it results in an improved health status and survival, including prevention of cardiovascular disease, life-long comorbid conditions, diverse complications and premature death in patients with CHD. In comparison to the general population, patients with CHD show decreased exercise capacity and a broad limitation of the ANS, involving a higher risk of mortality and morbidity. An improvement of exercise capacity, depending on cardiovascular and pulmonary factors, results in a decreased risk for hospitalization or death as well as in an increased health outcome and survival.

Therefore, the purpose of this dissertation was to outline exercise capacity in the context of training, heart rate variability and lung function in patients with CHD.

The specific aims of the three studies are as follows:

Study I:

(1) To make suitable recommendations for adult patients with CHD regarding physical activity.

Study II:

(1) To evaluate the parasympathetic activity in patients with various CHD to quantify the autonomic nervous system's activity.
(2) To examine a possible association of parasympathetic activity and exercise capacity in patients with CHD.

Study III:

(1) To investigate the effect of a telephone-supervised, daily inspiratory muscle training for six months on exercise capacity in adult patients with Fontan circulation.
(2) To investigate the effect of a telephone-supervised, daily inspiratory muscle training for six months on lung function in adult patients with Fontan circulation.

3 Background

3.1 Congenital heart diseases

Patients with CHD show a variety of anomalies which can be categorized as isolated shunts, isolated stenoses, stenoses and shunts, complex heart disease as well as uncommon congenital heart malformations. Heart defects may occur as isolated conditions or in association with further heart defects. Moreover, they are differentiated according to cyanotic or acyanotic condition. Isolated stenoses and shunts are almost never cyanotic, while a combination of them and complex CHD often result in cyanosis. Heart defects can be classified according to anatomical defects or cyanosis as well as to severity according to Warnes (see chapter 3.1.6).[12]

The current dissertation solely discusses those CHD whose data were collected within the context of the research part and whose hemodynamics are taken into account in the sports recommendations. In this chapter, neither the associated lesions nor the drug treatment of these diagnoses are considered. The individual diagnoses with their consequences, symptoms and interventions are presented exclusively, as they have a decisive influence on heart rate variability (HRV) and recommendations of exercise activities. In Study II the CHD were classified into four major subgroups consisting of “Left Heart Obstruction”, “Right Heart Obstruction”, “Transposition of the Great Arteries” and “Fontan Circulation” as well as a miscellaneous group. Since in Study III only patients with Fontan circulation were examined, the Fontan physiology is discussed in more detail to comprehend the effects of respiration and the absence of a missing subpulmonary ventricle in these patients.

3.1.1 Isolated shunts

Isolated shunts are central defects occurring at the veins, atria, ventricles and arteries and occur almost always on the same level of the right and left circulatory system.[49, 50] They are resulting in left-to-right shunting of blood, as the pressure is usually lower in the right than in its corresponding left compartment. A post-tricuspid shunt causes increased blood flow and particularly elevated pressure to the pulmonary circulation, while a pre-tricuspid shunt initially increases only blood flow.[49, 50] The size and anatomical position of the shunt as well as the pressure and the relative compliance of the chambers provide volume of blood shunting and the pressure in the pulmonary artery in case of a post tricuspid shunt.[49, 50] Isolated shunts represent the most common heart defect and for instance can be subgrouped into atrial septal defect (ASD), ventricular septal defect (VSD), partial or complete atrioventricular septal

defect (pAVSD, cAVSD) and patent ductus arteriosus (PDA), as well as rare defects like aortopulmonary window of partial abnormalous pulmonary venous return.[49, 50]

3.1.1.1 Atrial septal defect

ASD is a central defect above or, to variable degrees, above and below the atrioventricular valve and represents a persistent communication between the atria.[49] Based on the location ASD can be further subdivided into different types: Secundum ASD, primum ASD, superior sinus venosus defect, inferior sinus venosus defect and coronary sinus septal defect (Figure 2A).[50, 51]

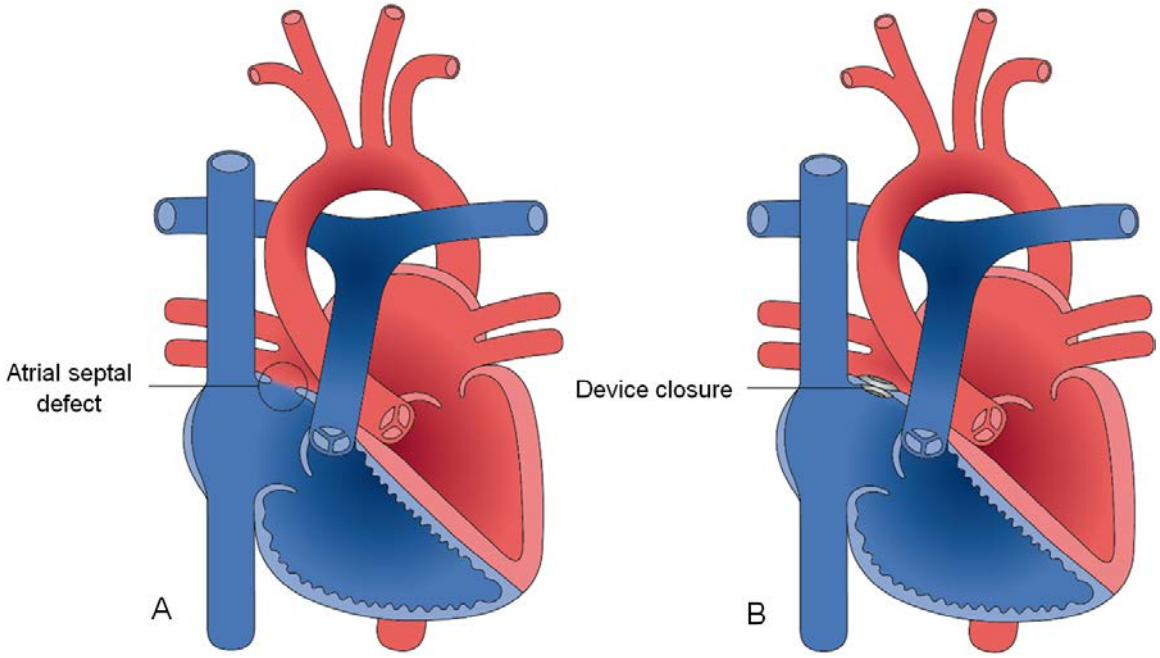

Figure 2: Atrial septal defect
A: Native secundum atrial septal defect; **B**: Device closure of secundum atrial septal defect. Modified from[52]

Hemodynamic changes depend on the ventricular compliances and atrial pressures, resistance in systemic and pulmonary vasculature and the location and size of the defect.[50, 53] While a small ASD has no hemodynamic consequences due to the small shunt, a large ASD, being associated with a large shunt, may cause essential hemodynamic consequences.[53] Compared to the left ventricle, the right ventricle has a higher compliance.[50] Hence, oxygenated blood is shunted from the left to the right atrium, causing volume overload and pulmonary overcirculation inducing dilation of the right atrium, right ventricle and pulmonary arteries.[49, 50, 53] Left-to-right shunting can be increased by reduced left ventricular compliance or elevated left atrial pressure and can be decreased by reduced right ventricular compliance or

tricuspid valve disease.[50] Ultimately, through decline of the right ventricle's compliance or failure, right-to-left shunting could appear resulting in cyanosis.[50]

Numerous of small ASD close spontaneously in early childhood or do not affect hemodynamic function, indicating no evidence of right ventricular overload, and thus do not need to be closed by surgery or catheter intervention.[49, 53] Commonly, patients with ASD remain asymptomatic until adulthood.[50, 54] Larger ASD with evidence on right ventricle volume overload cause symptoms in adulthood in the majority of patients including exertional shortness of breath, palpitations, reduced exercise capacity, fatigue, pulmonary infections and right heart failure.[49, 50, 54-57] With the age of the patient the pulmonary artery pressure increases which in turn increases the probability to suffer from tachyarrhythmia.[50] Atrial arrhythmias arise from the enlarged right heart and pressure overload. Atrial fibrillation or paradoxical embolism can cause systemic embolism.[49, 50] Thus, closure of the defects by catheter intervention or surgery influencing hemodynamic function is indicated to prevent long-term complications such as pulmonary vascular disease and dysfunction (Figure 2B).[49, 50]

3.1.1.2 Ventricular septal defect

VSD represents a defect within the interventricular septum, where several locations are possible: Perimembranous VSD, muscular VSD, outlet VSD and inlet VSD (Figure 3A).[49, 50, 58] Furthermore, multiple defects can occur simultaneously.[50] The spontaneous closure of small VSD occurs in the majority of defects.[58, 59] VSD that closed spontaneously in childhood or small defects that do not induce left ventricular volume overload do not need to be closed surgically or by catheter intervention, as they do not cause any symptoms.[53] The presence of symptoms and the degree of left ventricular volume overload are affected by residual shunt size.[49] The direction and extent of the isolated shunt are affected by the size of the defect, left and right ventricular systolic and diastolic function, pulmonary vascular resistance and the presence of right ventricular outflow tract obstruction.[49, 50, 53]

With increasing age of the patient VSD can result in left ventricle volume overload and heart failure, attributable to an increase in left ventricle systolic and diastolic pressure enlarging the left-to-right shunt.[50] Small VSD have a small left-to-right shunt, no left ventricle volume overload and no pulmonary arterial hypertension, as pulmonary blood flow is increased only minimally.[49, 50] Affected patients do not need treatment at all.[49, 50] Moderate VSD are associated with a small to moderate left-to-right shunt, mild to moderate left ventricle volume

overload and mild or no pulmonary arterial hypertension. These patients may develop no symptoms or have symptoms of mild congestive heart failure.[49]

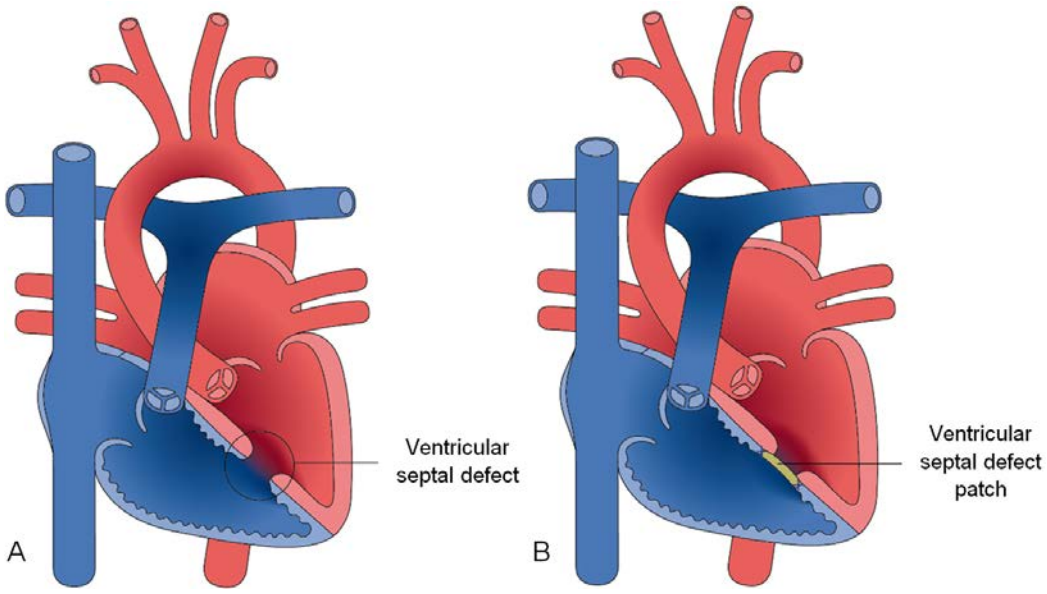

Figure 3: Ventricular septal defect
A: Native muscular ventricular septal defect; **B**: Patch closure of muscular ventricular septal defect. Modified from[52]

In contrast the majority of adult patients with large VSD will suffer from congestive heart failure in infancy, as large VSD involve a moderate to large left-to-right shunt, left ventricle volume overload and pulmonary arterial hypertension.[49] Since the pulmonary vascular resistance increases and the magnitude of left-to-right shunting declines, gradually the pulmonary vascular resistance equals or exceeds the systemic resistance, resulting in right-to-left shunting.[49, 53] Further, VSD can cause aortic valve prolapse, pulmonary hypertension and arrhythmias.[49, 50] Progressive development of pulmonary vascular disease can lead to exercise intolerance.[49] Large VSD and severe pulmonary vascular disease can result in right-to-left shunt and cyanosis, representing the Eisenmenger's syndrome (see chapter 3.1.3.2).[49, 50]

Large VSD should be surgically closed in the first six months of life. Smaller VSD can also be closed later by surgery or catheter intervention (Figure 3B). However, when severe irreversible pulmonary arterial hypertension has developed, VSD closure is not recommended in these patients.[53]

3.1.1.3 Atrioventricular septal defect

This group of defects can be described as AVSD, atrioventricular canal defect or endocardial cushion defect.[49, 50] The AVSD is a central defect above, or to variable degrees, above and

below the atrioventricular valve (Figure 4A).[49] The common atrioventricular annulus, guarded by five leaflets, covers both ventricles.[49, 50] AVSD can be further subdivided into a pAVSD and a cAVSD. The septal defect of the pAVSD is located at the atrial level, consisting of a primum ASD and a partial atrioventricular canal.[50] The posterior and anterior bridging leaflets are fused centrally, creating separate right- and left-sided orifices.[49, 50] The defect of the cAVSD is located in the crux of the heart and extends into both the interventricular and interatrial septum.[50] In this type the complete atrioventricular canal is affected, there is only one orifice and central fusion is non-existent.[50] The atrioventricular node is situated inferior and posterior to the coronary sinus and the bundle of His and the left bundle branch are located posteriorly.[50] This contributes to an abnormal activation sequence of the ventricles.

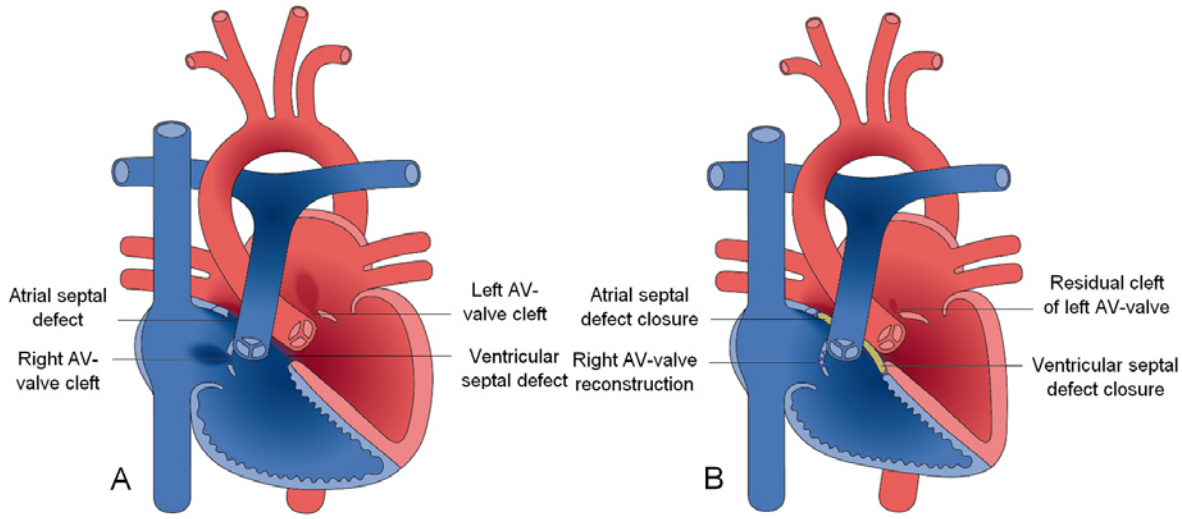

Figure 4: Atrioventricular septal defect
A: Native complete atrioventricular septal defect; **B**: Repaired complete atrioventricular septal defect
AV: atrioventricular. Modified from[52]

Hemodynamics are mainly conditioned on the presence and size of the VSD and ASD and competence of the left-sided atrioventricular valve.[49, 50] Shunting can range from small to large in these patients.[49] Arrhythmias, dyspnea, exercise intolerance, congestive heart failure, pulmonary arterial hypertension, cyanosis and also subaortic stenosis tend to increase with age.[49, 50] Patients with unrepaired pAVSD show clinical symptoms of an atrial left-to-right shunt and / or symptoms of left-sided atrioventricular valve regurgitation.[49, 50] For larger defects, the history of native cAVSD is comparable to that of a VSD, ending in Eisenmenger's syndrome.[50]

Defect closure and valve repair are usually conducted by surgery in early childhood (Figure 4B).[49]

3.1.1.4 Patent ductus arteriosus

PDA is the persistent communication between the proximal left pulmonary artery and the descending aorta, distal to the left subclavian artery (Figure 5A).[49, 50, 53] In the fetus the defect enables pulmonary arterial blood to enter the descending aorta for oxygenation in the placenta, bypassing the undeployed lungs. It usually closes shortly after birth.[53] When no spontaneous closure occurs, continuous flow from the aorta to the pulmonary artery remains.[53]

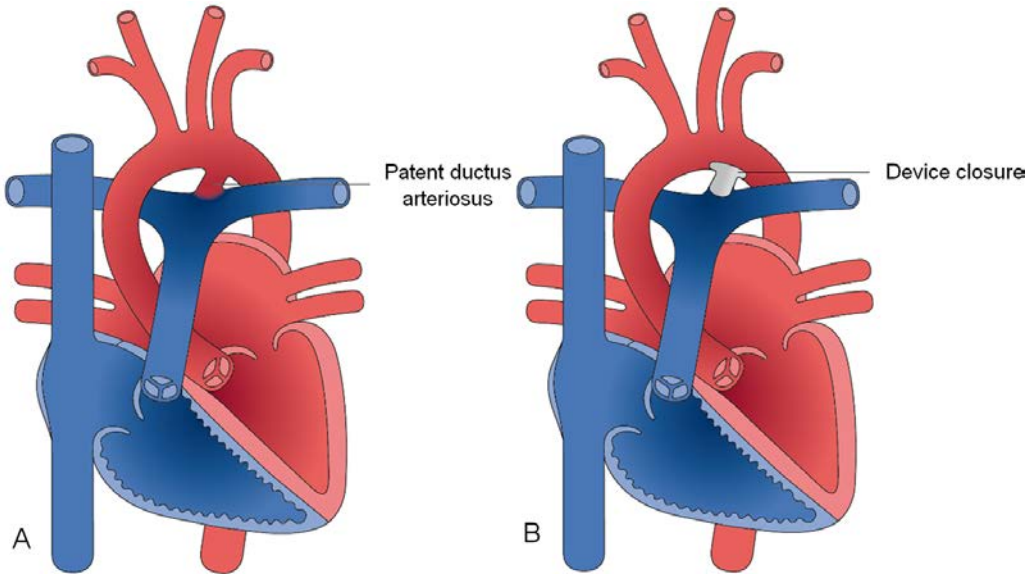

Figure 5: Patent ductus arteriosus
A: Native patent ductus arteriosus; **B**: Device closure of patent ductus arteriosus. Modified from[52]

Patients with a small duct, having no left ventricle overload and a normal pulmonary artery pressure, remain asymptomatic. Nevertheless, larger PDA result in left-to-right shunt and left ventricle volume overload.[50] In patients with moderate and large defect pulmonary pressure is elevated.[50] With age left ventricle volume overload or pulmonary arterial hypertension may develop, including easy fatigability, shortness of breath, dyspnea and palpitations.[49, 50, 60, 61] Patients are subjected to an enhanced risk of developing endarteritis, pulmonary vascular disease and heart failure.[49, 50, 61] Further, the defect may become calcified and aneurysmal, which may lead to its rupture.[49, 50, 62-64] Larger shunts increase blood flow causing left ventricular failure.[53] When pulmonary vascular resistance rises and exceeds systemic vascular resistance, right-to-left shunt appears.[60, 65] Accordingly, Eisenmenger's syndrome could emerge due to a large PDA.[49, 50]

PDA can be closed by surgery or catheter intervention (Figure 5B). Almost only patients who have an unsuitable anatomy or a ductus being too large for device closure undergo surgery.[49, 50, 53]

3.1.2 Isolated stenoses

Isolated stenoses are narrowings occurring for instance at the valve orifice, below or above the valve and obstruct blood flow to the arteries.[49, 50] Development of stenosis is often progressive resulting in compensatory ventricular hypertrophy, dilation or progressive ventricular dysfunction and sudden cardiac death.[49, 50, 53] Ventricular outflow tract obstructions can be divided into a left and right ventricular outflow tract obstruction. Left ventricular outflow tract obstruction includes valvular, subvalvular or supravalvular aortic stenosis (AS) and coarctation of the aorta (CoA).[66] Right ventricular outflow tract obstruction can further be diagnosed as valvular, subvalvular or supravalvular pulmonary stenosis (PS).[49, 50] Patients with AS, aortic insufficiency and CoA were classified into "Left Heart Obstruction" and patients with PS, pulmonary insufficiency and Tetralogy of Fallot (ToF) (see chapter 3.1.3.1) into "Right Heart Obstruction" in Study II.

3.1.2.1 Aortic stenosis

AS is a narrowing close to the aortic valve.[49, 50] This stenosis can occur at the aortic valve orifice, below or above the aortic valve and obstructs blood flow to the aorta. Based on the location, AS can be specified as valvular, subvalvular or supravalvular AS (Figure 6A).[49, 50] Bicuspid aortic valve represents the most common cause of congenital valvular AS, since it involves predominant obstruction or regurgitation of the blood flow to the aorta, depending on the degree of commissural fusion.[49, 50, 67-69] The bicuspid aortic valve is not necessarily stenotic at birth.[53] However, it is exposed to abnormal hemodynamic stress, which can lead to calcification and thickening of the leaflets and thus to immobility of the valve.[53] In the majority of patients with bicuspid aortic valve, the aortic wall shows abnormalities of smooth muscle, extracellular matrix, collagen and elastin and can lead to progressive dilation, aortic aneurysm or dissection.[49, 50, 67-69]

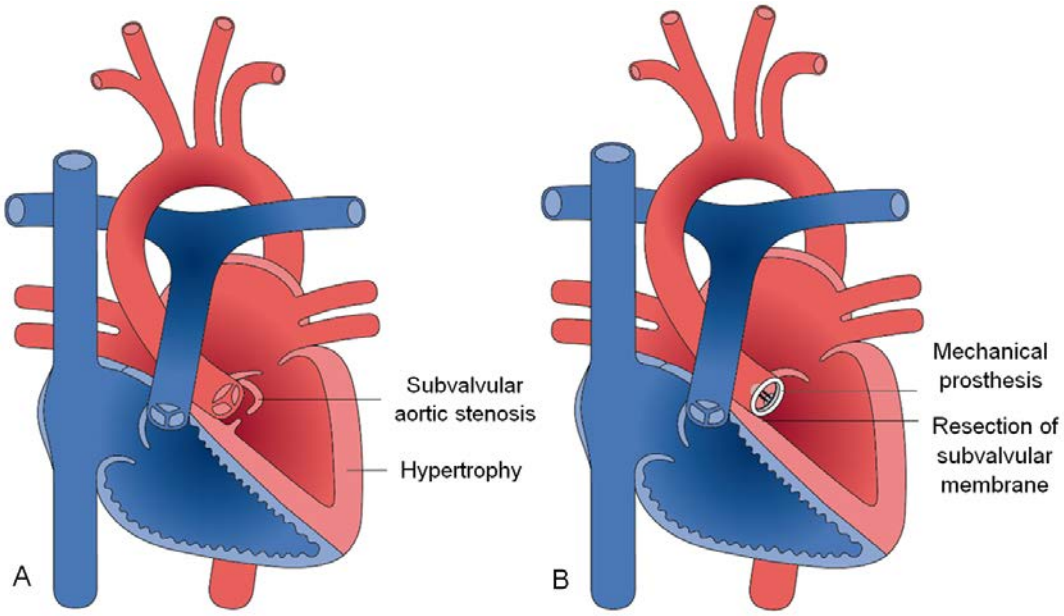

Figure 6: Aortic stenosis
A: Native subvalvular aortic stenosis, membranous type; **B**: Aortic valve replacement by using mechanical prosthesis and resection of subvalvular membrane. Modified from[52]

Subvalvular AS is a discrete fibrous ring or fibromuscular narrowing of the aorta.[50] This ring can frequently extend over the anterior mitral leaflet.[49] Occasionally, anomalous chords or accessory mitral tissue may cause subvalvular AS.[49] The development of subvalvular AS is often progressive.[49, 50] Hence, native condition includes progressive ventricular dysfunction, aortic valve damage and sudden cardiac death.[49] Obstruction and aortic regurgitation can also be detected in these patients.[49, 50, 70-72]

Supravalvular AS is a fixed obstruction developing directly above the sinus of Valsalva.[49, 73] It spreads a variable distance along the aorta and occurs, most commonly, as an external hourglass deformity with a pursuant luminal narrowing of the aorta.[49, 50, 73] Further it can arise as diffuse stenosis of the ascending aorta or as a localized fibrous diaphragm distal to the coronary artery ostia.[50] As the coronary arteries origin is commonly proximal to the obstruction, they are exposed to high systolic pressure and limited diastolic flow.[49, 50, 73] Aneurysm or ectasia of the coronary arteries as well as partial or complete ostial obstruction of the coronary arteries could develop.[73] In adulthood, coronary artery disease as well as significant coronary insufficiency can occur.[49, 74, 75] This may be due to pathological histologic changes with intimal and medial fibrosis, dysplasia, hyperplasia, occasional intramedial dissection and adventitial fibroelastosis, which are diagnosed particularly in adults.

Patients with AS often remain symptom-free for many years.[49, 50] The progression of the stenosis differs and is affected by atherosclerotic risk factors, age, degree of calcification and the initial severity.[50] Severity is classified as mild, moderate, or severe.[49, 76] If the valve area is reduced, AS with mild severity can also become hemodynamically important. General symptoms of AS are dyspnea, angina pectoris, syncope or near-syncope, aortic dissection, dilated ascending aorta or aortic sinuses and heart failure.[49, 50, 53] The median survival is only five years after appearance of angina, three years after occurrence of syncope and two years after development of symptoms of heart failure.[77] Once symptoms occur prognosis deteriorates rapidly.[53] Therefore, patients with symptomatic AS should undergo valve replacement, if clinically possible (Figure 6B).

Balloon valvuloplasty, valve replacement and Ross procedure represent potential interventions in patients with AS.[49, 50] While balloon valvuloplasty can be successfully performed in children, adolescents and young adults with non-calcified valves, valve replacement is recommended for patients with calcified valves.[49, 50, 78] The Ross procedure is a more encompassing procedure, representing a two-valve operation.[79] For this surgery the pulmonary valve is used as an autograft for the aortic valve, and a new biological valve is implanted in pulmonary position.[49] It has been proposed for patients who want to avoid anticoagulation and for those of childbearing age, yet it implies a significant re-operation rate after the first postoperative decade.[49, 50] The Ross procedure is still the preferred surgery for children when a balloon dilatation or a valve plastic cannot be performed.

3.1.2.2 Coarctation of the aorta

CoA is not just a circumscribed narrowing of the aorta and can also be considered as a part of a generalized arteriopathy.[50] CoA develops as a long, hypoplastic aortic segment or as a discrete stenosis and is usually located at the insertion of the ductus arteriosus, in the region of the ligamentum arteriosum contiguous to the origin of the left subclavian artery (Figure 7A).[49, 50, 53] Rarely it occurs ectopically, such as at the ascending, descending or abdominal aorta.

CoA leads to an increased left ventricular afterload, causing increased wall stress and compensatory left ventricular hypertrophy.[50] Left ventricular dysfunction and arterial collaterals proximal to the obstruction, through the internal, subclavian, scapular, thoracic and intercostal arteries, can be developed.[49, 50, 53] Further consequences are increased pressures and potentially dilation of the left heart, resulting in high blood pressure in the upper part and

low blood pressure in the lower part of the body.[49, 50, 53] Complications of CoA include hypertension, premature coronary artery disease, aortic dissection and dilatation as well as cerebrovascular accidents, infective endocarditis and left ventricular failure.[49, 53]

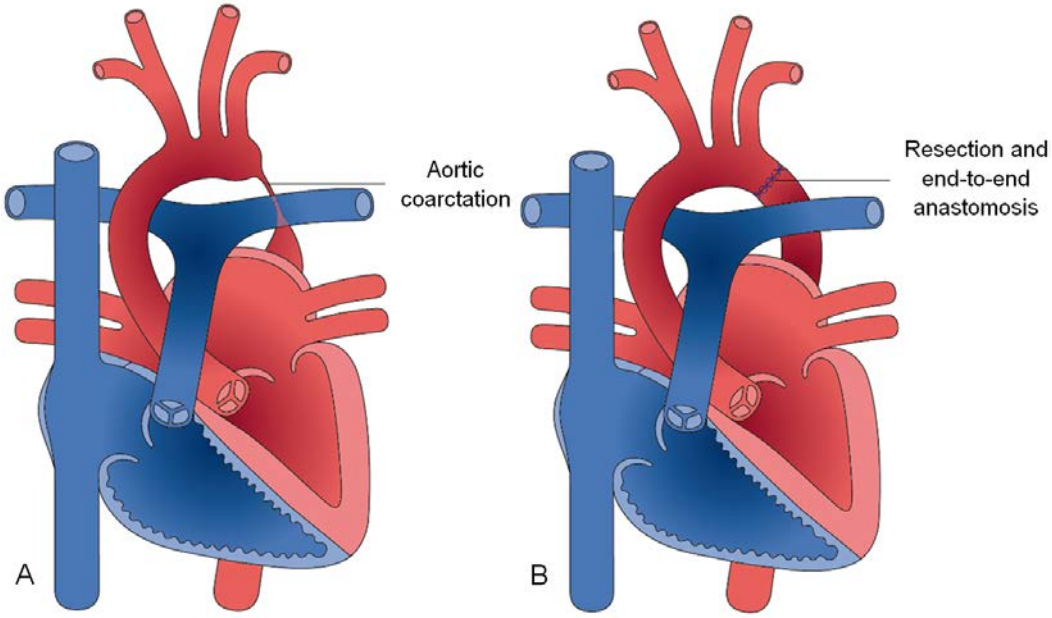

Figure 7: Coarctation of the aorta
A: Native aortic coarctation, tubular type; **B**: Aortic coarctation repair by resection and end-to-end anastomosis. Modified from[52]

Signs and symptoms are associated with respective severity.[50] Since majority of concerned patients is asymptomatic, CoA is diagnosed during routine physical examination, due to discrepant upper and lower extremity pulses.[49, 53] Serious CoA cause signs and symptoms even before reaching adulthood including headache, palpitations, dizziness, tinnitus, systemic hypertension, epistaxis, abdominal angina, cold feet, leg cramps, claudication, exertional leg fatigue and shortness of breath.[49, 50, 53]

Potential interventions in patients with CoA are surgical repair or catheter based interventions including angioplasty with and without stenting if anatomy is appropriate (Figure 7B).[49, 50, 80] The patient's age at the time of intervention affect both the incidence of persistent or recurrent hypertension and the survival rate.[53] CoA is not a localized disease of the aorta, but accompanied with a pathological vessel wall structure leading to vascular malformations like aneurysm, especially in the ascending aorta and the brain.[50, 81, 82]

3.1.2.3 Pulmonary stenosis

PS is a narrowing close to the pulmonary valve.[49] This stenosis can occur at, below or above the pulmonary valve and obstructs blood flow to the pulmonary arteries.[49] Based on the

location, PS can be specified as valvular, subvalvular or supravalvular PS (Figure 8A).[49] Valvular PS typically is an isolated abnormality.[49, 53] A dysplastic valve can be found in approximately 20% of patients with valvular PS.[49, 83, 84] Valvular malformations, implicating immobile, thickened, displastiv leaflets and composing myxomatous tissue, can be divided into three morphological types: Typical dome-shaped pulmonary valve, dysplastic pulmonary valve and unicuspid or bicuspid pulmonary valve.[49, 50, 53] Subvalvular PS can be further divided into infundibular and subinfundibular stenosis, since obstruction can be located at both levels below the pulmonary valve.[49, 50, 85] Supravalvular PS can be situated in the main branches or more peripherally, caused by narrowing of the pulmonary trunk, pulmonary arterial bifurcation or pulmonary branches.[49, 50, 53]

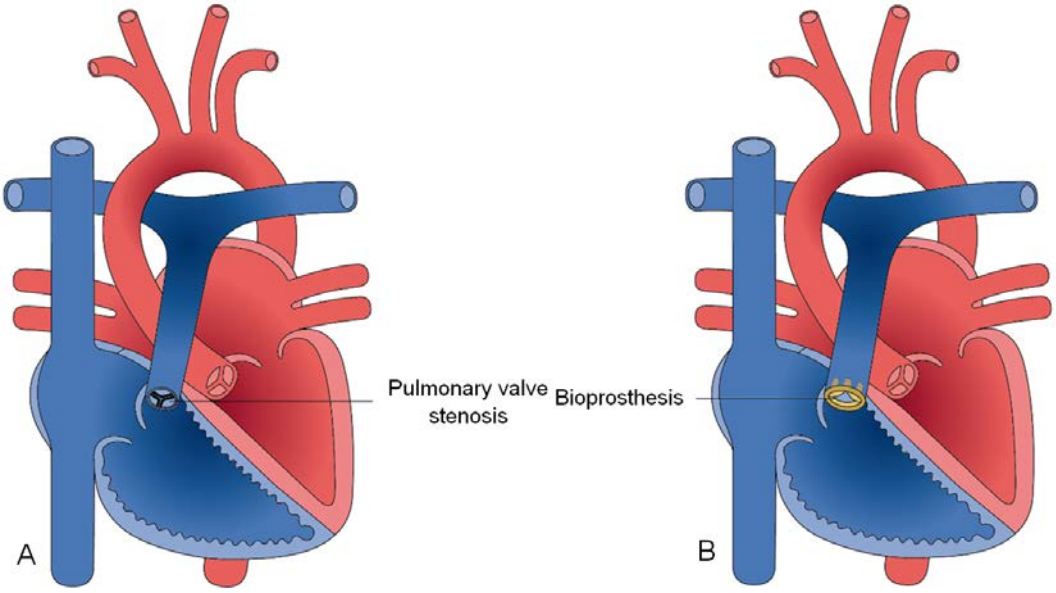

Figure 8: Pulmonary stenosis
A: Native pulmonary valve stenosis; **B**: Pulmonary valve replacement by bioprosthesis valve. Modified from[52]

Severity of PS is classified as mild, moderate or severe. Severity of stenosis, competence of the tricuspid valve and right ventricular systolic function determine absence or presence of symptoms, their severity and the patient's prognosis of survival.[53] PS can progress in severity due to reactive myocardial hypertrophy.[49] Patients with PS are often asymptomatic, particularly patients with mild to moderate severity.[49, 50, 53] Dyspnea, fatigability, reduced exercise capacity, dizziness, syncope, angina symptoms and right ventricular dilation or failure occur especially in patients with severe PS, having a worse prognosis.[49, 50, 53] Finally, cyanosis and systemic venous congestion could arise in these patients.[49, 53]

Surgery and balloon valvuloplasty are potential interventions in patients with PS. For patients suffering from infundibular PS and hypoplastic pulmonary annulus, subinfundibular PS,

dysplastic pulmonary valves or associated lesions surgery is recommended.[49, 50] In patients with valvular PS and with peripheral PS with valves which are not dysplastic, relief of stenosis can be accomplished through catheter intervention.[50, 53] Valve replacement may be recommended for patients with PS and significant valvular regurgitation (Figure 8B).[49]

3.1.3 Stenoses and shunts

Stenoses, which are obstructing blood flow to the arteries, and shunts, enabling interventricular or interatricular shunting of blood and therefore causing increased blood flow to the ventricles and arteries or atria and veins, can occur together in CHD.[49, 50] In these defects prestenotic shunts eliminate obstruction before stenoses, while poststenotic shunts ensure perfusion behind stenosis. Anomalies differ in severity and morphological spectrum.[49] The options of treatment and correction vary not only with regard to the individual CHD, but also with respect to their particular malformation, severity and progression.[49, 50] Two CHD exhibiting stenoses and shunts are ToF and Eisenmenger's syndrome.[86] Patients with ToF were classified into "Right Heart Obstruction", while patients with Eisenmenger's syndrome were assigned to the miscellaneous group in Study II.

3.1.3.1 Tetralogy of Fallot

ToF encompasses a large VSD, an aorta that overrides both ventricles, right ventricular outflow tract obstruction and consequent right ventricular hypertrophy (Figure 9A).[49, 50, 86] Due to the VSD, which is located in the subaortic position, the right and left ventricular pressures are equal.[49, 86] In addition, flow resistance increases in the right ventricular outflow tract, resulting in substantial right-to-left shunting.[86] Severity of right ventricular outflow tract obstruction, which may be valvular, infundibular or a combination of both, with or without supravalvular or branch pulmonary artery stenosis, determines the magnitude of shunting.[49, 85] Abnormalities of the pulmonary artery are common and may involve stenosis and hypoplasia, including the pulmonary trunk or the branch pulmonary arteries.[49] The pulmonary valve is stenotic and small in most cases. There can be varying degrees of severity of all characteristics.[49] Pulmonary atresia with VSD represents the most severe form of ToF.[49]

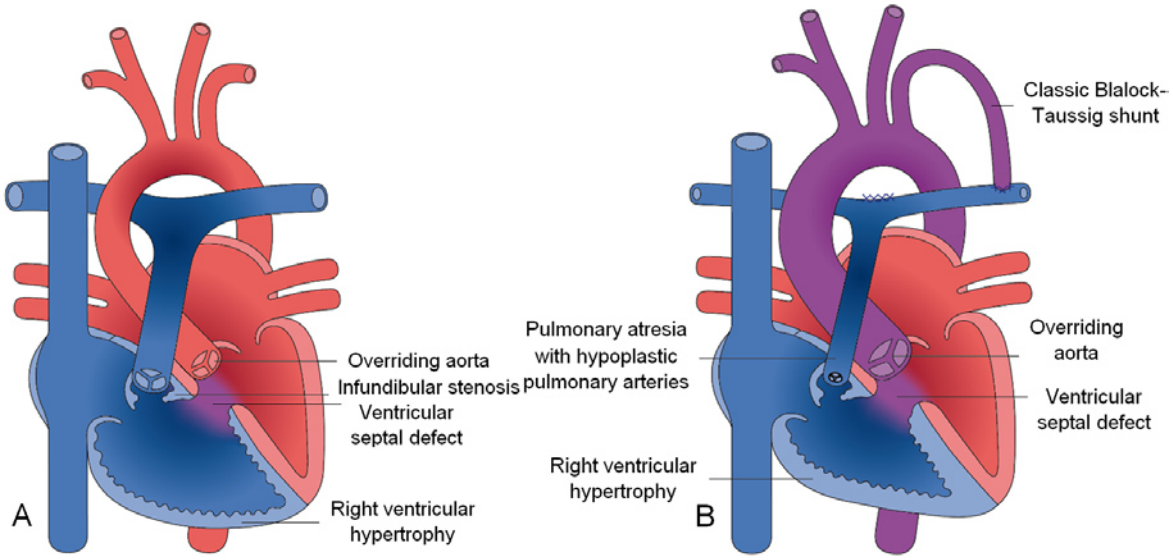

Figure 9: Tetralogy of Fallot
A: Native tetralogy of Fallot; **B**: Tetralogy of Fallot with Blalock-Taussig shunt left. Modified from[52]

In childhood, patients suffer from cyanosis, tachypnea, hyperpnea, loss of consciousness or even death.[50, 86, 87] Adults with ToF have dyspnea and limited exercise tolerance, cyanosis, including erythrocytosis, abnormalities of hemostasis and stroke.[88] Since majority of these patients suffers from progressive cyanosis, palliative procedures aim to increase pulmonary blood flow resulting in an improved survival.[49, 86] Some infants need palliative surgery involving anastomosis of systemic artery to pulmonary artery. Blalock-Taussig procedure implicates an end-to-side anastomosis of the subclavian artery to the pulmonary artery, Waterson procedure includes a side-to-side anastomosis of the ascending aorta and the right pulmonary artery and Potts procedure results in a side-to-side anastomosis of the descending aorta to the left pulmonary artery (Figure 9B).[50, 86, 89] These procedures are followed by surgical procedures for repair including primarily VSD closure and relief of right ventricular outflow tract obstruction, but also replacement of ascending aorta for dilatation and tricuspid valve repair or replacement.[49, 50] In palliated patients with favorable pulmonary artery anatomy and reversible pulmonary arterial hypertension complete repair can be considered already in infancy.[50, 90, 91]

Patients are generally asymptomatic after surgery.[49, 86] Nevertheless, these surgeries are associated with long-term complications like residual right ventricular outflow tract obstruction and residual VSD that may result in left ventricular volume overload and dysfunction as well as in right ventricular dilation and dysfunction.[49, 50] The latter could evolve as a sequel to significant pulmonary regurgitation, developing especially after

transvalvular patch repair in most cases.[49] Besides, aortic root dilation with aortic regurgitation, tachycardia and sudden cardiac death could occur in patients with ToF.[49, 92]

3.1.3.2 Eisenmenger's syndrome

Eisenmenger's syndrome is defined as a CHD with initially large left-to-right shunt, consequently causing severe pulmonary vascular disease and pulmonary arterial hypertension, resulting in right-to-left shunt and central cyanosis (Figure 10).[50, 86, 93] The development of pulmonary arterial hypertension is determined by the type and size of the underlying anatomic defect and the magnitude of shunt flow.[49, 86] Accordingly, pulmonary arterial hypertension arises through high pulmonary vascular resistance, caused by shear stress from volume or pressure overload in the pulmonary arteries.[50] This progressive increase in pulmonary vascular resistance can cause subpulmonary ventricular failure and death.

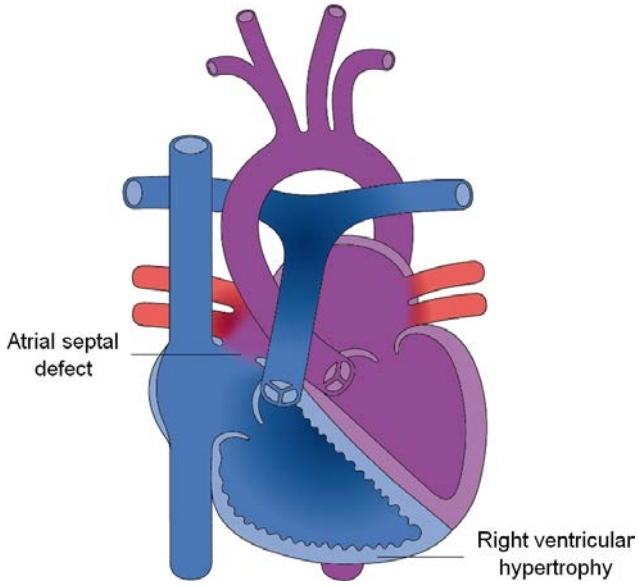

Figure 10: Eisenmenger's syndrome
Eisenmenger's syndrome with atrial septal defect. Modified from[52]

Eisenmenger's syndrome, which represents the end stage of this progressive vascular disease, is a multiorgan disorder with progressive deterioration in time.[50] Morphologic changes usually begin in childhood, but symptoms may not appear until late childhood or early adulthood, so impaired exercise tolerance and exertional dyspnea may be well compensated for years.[86, 94] Patients with Eisenmenger's physiology suffer from fatigue, hyperpnea, dyspnea on exertion, palpitation, syncope, edema, cardiac ischemic chest pain, hypoxemia and progressive cyanosis.[50, 93, 95, 96] Furthermore, progressive subpulmonary ventricular failure and premature death are common in adults with Eisenmenger's syndrome.[50, 93, 96] If surgery is

performed before pulmonary vascular changes are irreversible, the changes that occur in shunt-mediated pulmonary arterial hypertension are reversionary and Eisenmenger's syndrome can be prevented.[49]

3.1.4 Complex heart diseases

Complex heart diseases include a large number of malformations resulting from malconnections of various vascular or cardiac segments with or without shunts and stenoses.[49, 50] In transposition of the great arteries (TGA) ventriculo-arterial discordance exists, where shunts are inevitable, since a communication between the two circuits is a prerequisite for survival.[86] Ventriculo-arterial discordance and atrioventricular discordance with structural anomalies like VSD or PS exist in congenitally corrected transposition of the great arteries (ccTGA).[49, 50] In most cases a complete separation of the systemic and pulmonary circulations exists. Nevertheless, the morphological right ventricle needs to serve as the systemic ventricle.[86] In study II, the "Transposition of the Great Arteries" group consisted of patients with TGA and ccTGA.

Malformations which are not suitable for biventricular repair are referred to as univentricular hearts (UVH). Palliative procedures result in the flow of systemic venous blood to the lungs without interposition of a pumping ventricle, regardless of the ventricular morphology.[97] CHD exhibiting these malformations lead to long-term complications including arrhythmias, fatigue, exercise intolerance, dyspnea, cyanosis, pulmonary and chronic systemic venous hypertension, ventricular dysfunction, heart failure as well as sudden cardiac death and therefore have a major impact on morbidity and mortality.[32, 49, 50, 98-100] Due to their incomparable physiology, a group was created exclusively for patients with Fontan circulation in Study II. Based on its modifications, the Fontan circulation can be further classified into atriopulmonary anastomosis (APA), atrioventricular anastomosis (AVA) and total cavopulmonary connection (TCPC). The study patients of Study III exhibit these different physiologies. For better traceability, the individual surgical steps are explained in detail in this chapter.

3.1.4.1 Transposition of the great Arteries

TGA implicates a ventriculo-arterial discordance with an atrioventricular concordance.[49, 50] The aorta arises from the right ventricle, rightward and anterior to the pulmonary artery. The left ventricle gives rise to the pulmonary artery.[50] These two parallel circulations indicate a

complete separation of the systemic and pulmonary circulations.[86] This manifestation is called simple TGA, since no significant additional cardiac lesions are present (Figure 11A).[50] A communication between the two circuits is a prerequisite for survival.[49, 86] In these patients the PDA and foramen ovale enable communication between the systemic and pulmonary circulations. Nevertheless, severe cyanosis is present.[86] A complex TGA shows in addition to the ventriculo-arterial discordance intracardiac anomalies including VSD, left ventricular outflow tract obstruction and CoA, enabling intracardiac mixing.[49, 50] Based on left-to-right shunting there is a less severe cyanosis, but an increased risk for left ventricular failure caused by volume overload.[86]

Fundamentally, there are two possibilities to treat a TGA through heart surgery. The atrial switch operation according to Senning or Mustard, physiologically corrects the heart defect and the arterial switch operation results in an anatomical correction. Both procedures of physiological correction were developed almost simultaneously. During this operation the atrial septum was excised.[86, 101] A baffle within the atria was constructed to divert pulmonary venous blood to the tricuspid valve and the right ventricle.[49] The systemic venous blood was also diverted through a baffle to the mitral valve and to the left ventricle.[49] After the procedure, the left ventricle remains on the pulmonary artery and the right ventricle remains attached to the aorta. The atrial switch operations according to Senning or Mustard involve correct blood flow and therefore abolishes cyanosis and enables survival.[86] However, the right ventricle is responsible for pumping the blood through the systemic circulation and the great arteries remain reversed (Figure 11B).[86] Accordingly, right ventricular dysfunction and systemic tricuspid regurgitation occur, having a major impact on morbidity and mortality.[50, 102, 103] Structural complications include baffle leaks, implicating left-to-right or right-to-left shunt, and obstructions, which may lead to venous congestion into the lungs or into the systemic veins.[49, 50] Further, patients who underwent atrial switch operation may suffer from PS, residual VSD, sinus node dysfunction and tachyarrhythmias.[49, 50, 104] The latter are associated with sudden cardiac death.[105] Decreased exercise capacity is observed in most patients.[106]

The arterial switch operation replaced the atrial switch operation, still being the method of choice today. For this anatomical correction, the great vessels are transected above the semilunar valves and coronary arteries, switched and reconnected.[86] The aorta is connected to the former pulmonary valve, arising from the left ventricle. The pulmonary artery is connected to the former aortic valve, arising from the right ventricle.[86] Also the coronary

arteries supplying the heart with blood need to be disconnected and reattached to the neoaorta to restore normal coronary circulation (Figure 11C).[86] The result is an anatomically correct circulatory situation being associated with an excellent long-term outcome. Nevertheless, long-term complications include myocardial ischemia, coronary insufficiency, left ventricular dysfunction and arrhythmias, supravalvular PS, aortic dilation and aortic or pulmonary regurgitation.[49, 50] Further, due to positioning of the pulmonary bifurcation anterior to the ascending aorta, unilateral or bilateral pulmonary branch stenosis may occur.[50]

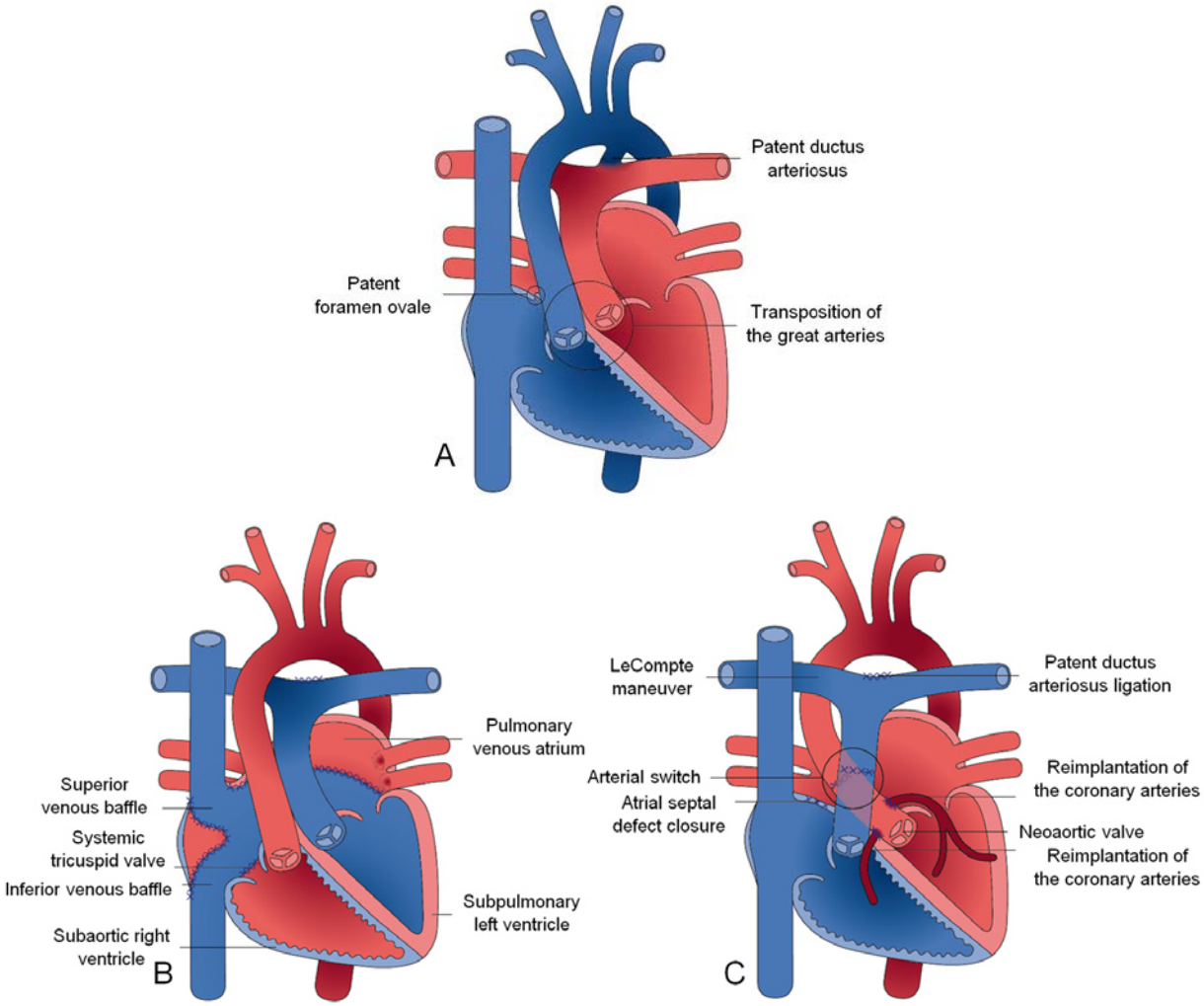

Figure 11: Transposition of the great arteries
A: Native simple transposition of the great arteries; **B**: Atrial switch operation (Senning / Mustard procedure); **C**: Arterial switch operation (Jatene procedure). Modified from[52]

TGA can also occur in a congenitally corrected form. This heart defect implicates ventriculo-arterial discordance and atrioventricular discordance (Figure 12).[49, 50] The aorta arises anteriorly from the morphological right ventricle which is connected to the left atrium. The pulmonary artery arises posteriorly from the morphological left ventricle which is connected to the right atrium.[50, 107] Thus, the morphological right ventricle serves as the systemic ventricle and the morphological left ventricle as the pulmonary ventricle. The two existing

discordances enable physically normal direction of blood flow.[49] For this reason, this manifestation of the TGA is called congenitally corrected.[108] Common associated structural anomalies are mainly VSD, PS and abnormalities of the systemic tricuspid valve.[49, 50]

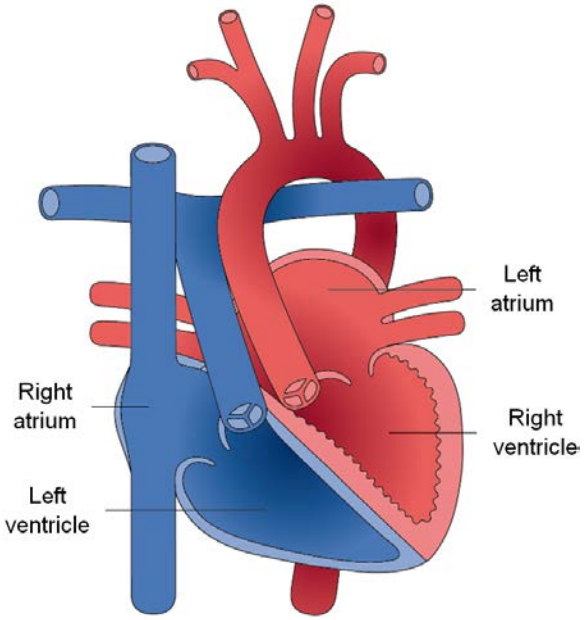

Figure 12: Congenitally corrected transposition of the great arteries
Native congenitally corrected transposition of the great arteries. Modified from[52]

Depending on the presence and severity of associated lesions, patients suffer to varying degrees from systemic atrioventricular valve regurgitation, fatigue, exercise intolerance, dyspnea, increasing cyanosis, atrioventricular condunction problems, arrhythmias, syncope, ventricular dilation and dysfunction as well as heart failure and congestive cardiac failure.[49, 50]

The onset of symptoms due to associated systemic atrioventricular valve regurgitation or morphological right ventricular dysfunction indicates surgery in adult patients with ccTGA.[49, 50] Since the morphological right ventricle is not suitable for a long-term function as a systemic pump, the aim is to convert the left ventricle to the systemic ventricle.[50] As the tricuspid valve is commonly morphologically abnormal, systemic atrioventricular valve replacement is one of the most surgical treatments in these patients. Pulmonary arterial stenosis or conduit stenosis can be dilated or stented by catheter intervention. However, systemic tricuspid valve regurgitation and dilated systemic right ventricle could benefit from residual left ventricular outflow tract obstruction due to septal shift.[50] Corrective surgery by double switch or atrial switch and Rastelli operation has proven feasible in children. Double switch operation includes atrial and arterial switch, while atrial switch and Rastelli operation involve implantation of an intraventricular rerouting conduit.[49] Since the mortality rate is high in

adults, the results remain uncertain and the procedure is considered controversial in infancy and childhood.[109]

3.1.4.2 Univentricular heart

The term "univentricular heart" includes a large number of malformations that are not amenable to biventricular repair, as either one ventricle is hypoplastic or cannot be connected surgically or interventionally in a useful sequence.[49, 50] Associated malformations are double-inlet left ventricle, tricuspid or mitral atresia and hypoplastic left heart syndrome (Figure 13A).[49, 50, 110] Functional univentricular anomalies with a dominant and an underdeveloped ventricle are implied in the term and the vitia are assigned to a morphological left or right ventricle. Abnormalities that are categorized to functional UVH are for instance pulmonary atresia with intact ventricular septum, complex forms of AVSD, ccTGA and double-outlet right ventricle.[49, 50] Additional intra- and / or extracardiac lesions such as isolated shunts, isolated stenoses, arch anomalies, malpositions of the great arteries, discordant connections, ventricular outflow tract obstructions and atrioventricular valve stenoses, regurgitations, overridings as well as straddlings are invariably concomitant with these conditions (Figure 13B).[49]

Initially, the single ventricle, which functions independently of its morphology as a systemic ventricle, supplies the systemic as well as the pulmonary circulation. Both circuits are not connected in series, but in parallel, resulting in a considerable volume load on the single ventricle.[110] In addition, there is a pronounced mixing of the systemic venous and the pulmonary venous inflow at atrial or ventricular level.[110] Clinical manifestation is essentially determined by the proportion of systemic and pulmonary blood flow.[110] Hemodynamically, a general categorization can be made between no anatomic restriction to pulmonary blood flow and obstruction to pulmonary blood flow.[49, 50]

Fontan surgery has become the most frequently used surgical approach for patients with UVH, where a biventricular correction is not feasible.[49, 50, 110] This procedure results in the flow of systemic venous blood to the lungs without interposition of a pumping ventricle.[49, 50, 97] Pulmonary arterial resistance and the function of the single ventricle represent the decisive selection criteria for Fontan surgery.[111] Together with the valve function, they are the essential determinants of long-term Fontan circulation.[110] This palliative surgery targets a separation of the systemic and pulmonary circulation, leading to a volume relief of the systemic ventricle,

as central venous blood is passed directly into the pulmonary circulation.[97, 110] Additionally, cyanotic condition and hemodynamic function are improved.[110]

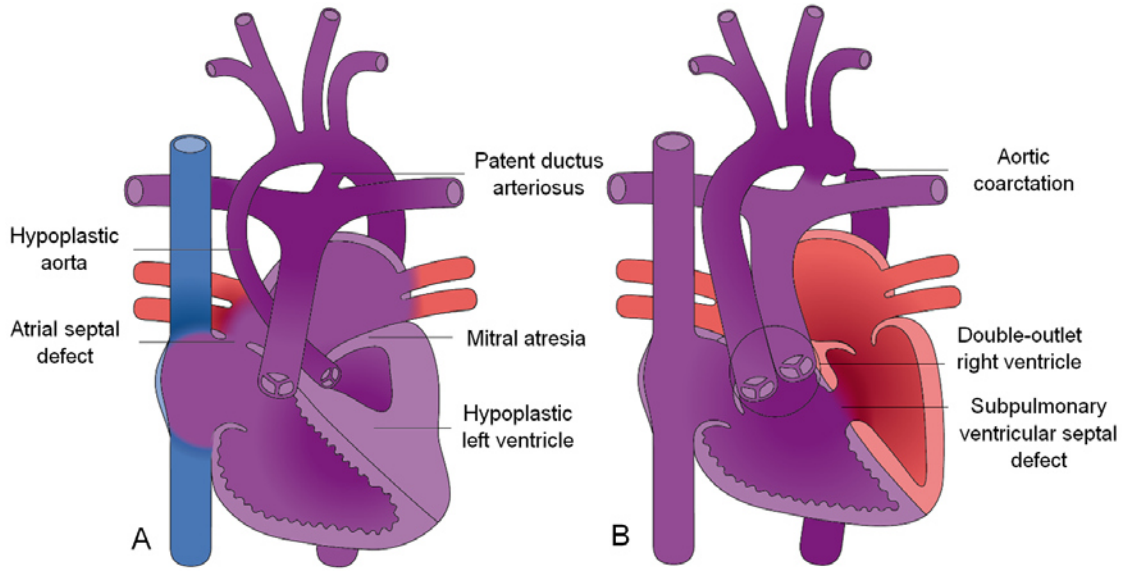

Figure 13: Univentricular heart
A: Univentricular heart: Mitral atresia and hypoplastic left ventricle; **B**: Functional univentricular heart: Double-outlet right ventricle with subpulmonary ventricular septal defect (Taussig Bing) and aortic coarctation. Modified from[52]

Conversion to the Fontan circulation is nowadays performed in multistage procedures allowing the patient's body to adapt to the different hemodynamic states and considerably reducing the mortality rate of the surgical intervention (see chapter 3.1.4.2.1 till 3.1.4.2.3).[110, 112] Since the study patients of the study III underwent modifications of the original Fontan surgery, these procedures are also explained subsequently (see chapter 3.1.4.2.4).

3.1.4.2.1 Stage one

Regulation of pulmonary blood flow represents the treatment objective of the first surgical intervention, since lung perfusion under native condition can either be drastically reduced or increased.[110] Patients with obstruction to pulmonary blood flow have a very constrained pulmonary blood flow, commonly caused by valvular or subvalvular PS or atresia and resulting in cyanosis.[49, 50, 110] Reduced or no pulmonary blood flow should be avoided to enable the development of pulmonary arteries postpartum and to prevent pronounced cyanosis.[110] A modified Blalock-Taussig shunt from the brachiocephalic truncus to the ipsilateral pulmonary artery or a central shunt from the ascending aorta to the pulmonary artery may result in sufficient pulmonary perfusion (Figure 14A).[110]

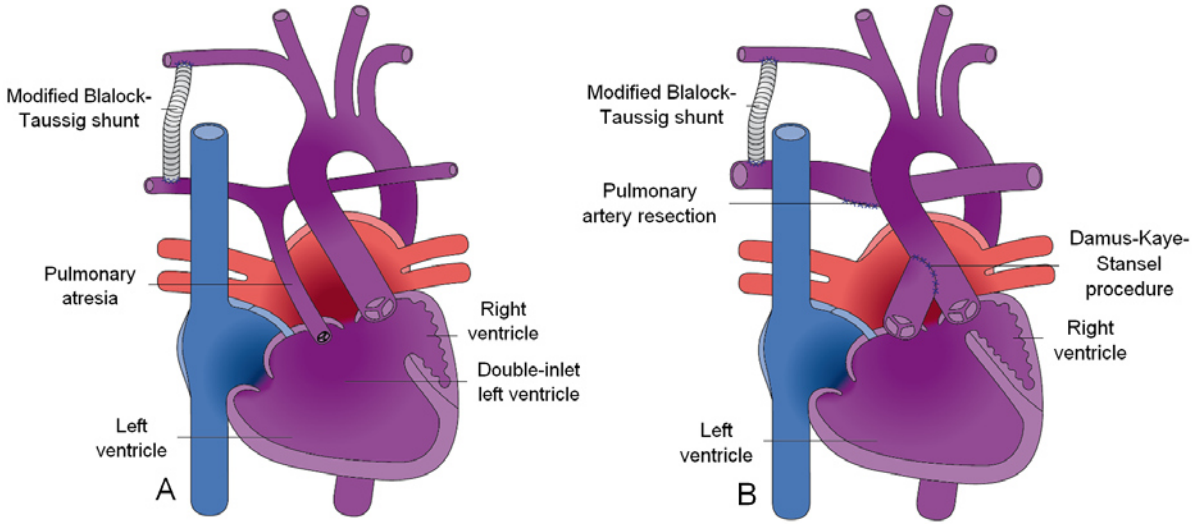

Figure 14: Blalock-Taussig shunt and Damus-Kaye-Stansel procedure
A: Modified right Blalock-Taussig shunt for double-inlet left ventricle; **B**: Damus-Kaye-Stansel procedure with modified right Blalock-Taussig shunt for double-inlet left ventricle. Modified from[52]

Patients with no anatomic restriction to pulmonary blood flow develop large left-to-right shunt with heart failure and on long-term pulmonary vascular disease.[49] To reduce any systemic outflow obstruction and to limit pulmonary blood flow, surgical treatment is required at an early age.[49] For the reduction of pulmonary hyperperfusion and AS, Damus-Kaye-Stansel surgery should be performed, resulting in a stenosis free flow through the former pulmonary valve to the aorta and a controlled pulmonary perfusion (Figure 14B).[49, 110] This is achieved by depositing the pulmonary artery shortly before bifurcation, anastomosis of the proximal end of the transected pulmonary artery in an end-to-side fashion to the ascending aorta, and applying an aortopulmonary shunt.[110]

After this early palliation, transformation into a kind of Fontan circulation is needed. Usually, this is a twostep procedure, initially including direct anastomosis of the right atrium to the main pulmonary artery.[110]

3.1.4.2.2 Stage two

The second procedure is the partial cavopulmonary connection (PCPC), consisting of Glenn procedure or hemi-Fontan operation, and preferably should be performed after the third month of life.[49, 50, 110] The transfer of the parallel circulation into the PCPC circulation represents the main relief for the heart, which is volume-loaded caused by the parallel circulation.[110] A low pulmonary arterial resistance and sufficiently large pulmonary arteries are the basic prerequisites for these procedures.[110] Bidirectional Glenn anastomosis involves the resection of the aortopulmonary shunt at the heart-lung machine on the beating heart with end-to-side

anastomosis of the superior vena cava to the right pulmonary artery, resulting in superior vena cava blood being directed to both right and left pulmonary arteries.[110] A potentially present left persisting superior vena cava without a bridge vein connection to the right superior vena cava must be anastomosed with the left pulmonary artery in the same way (Figure 15).[110]

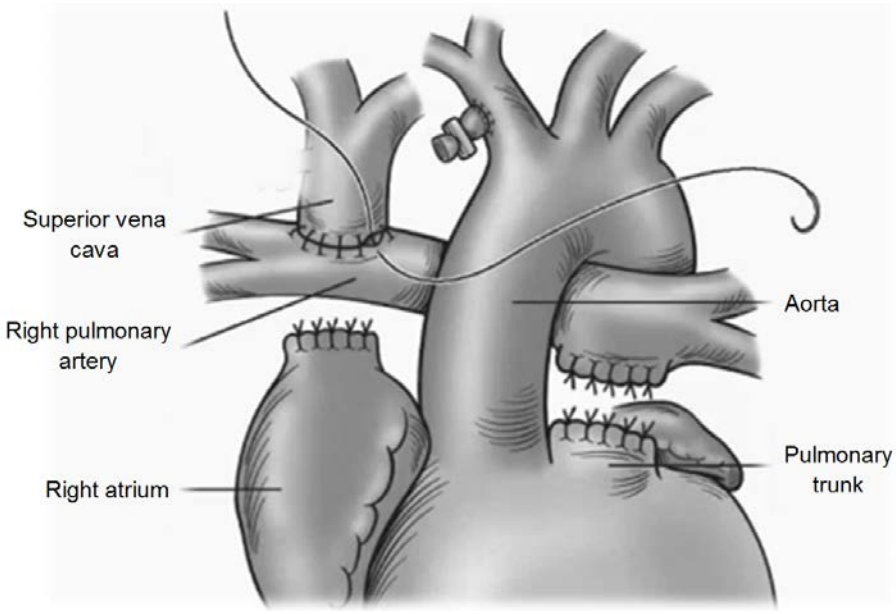

Figure 15: Glenn anastomosis
Modified from[113]

Hemi-Fontan surgery is considered as an alternative to the Glenn procedure and as preparation for Fontan palliation and involves the construction of an intraatrial lateral tunnel.[110] It is more complex than the bidirectional cavopulmonary shunt since it includes both an atriopulmonary anastomosis (APA) between the dome of the right atrium and the underside of the right pulmonary artery as well as a placement of a Gore-Tex patch, which is placed in the superior aspect of the right atrium.[110] The latter directs blood flow from the superior vena cava atriocaval junction into the APA and augments central pulmonary artery area, since it usually extends into the left pulmonary artery behind the aorta (Figure 16).[112, 114]

The hemi-Fontan physiology corresponds to that of the bidirectional Glenn shunt, yet cyanosis is not improved in both physiologies.[110] For the later intracardiac TCPC only the superior vena cava patch needs to be removed and the intracardiac tunnel needs to be completed with a patch in patients with hemi-Fontan physiology.[110, 112]

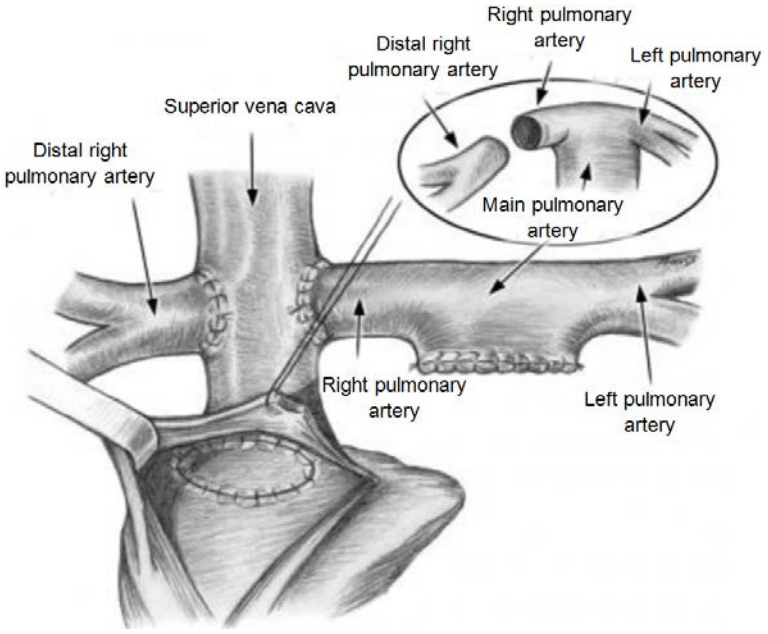

Figure 16: Hemi-Fontan surgery
Modified from[113]

3.1.4.2.3 Stage three

TCPC involves the final separation of the circulatory system with elimination of cyanosis, apart from a small residual shunt via the coronary sinus, and is performed in patients aged 18-24 months with a minimum weight of 10 kg.[110, 115] Ideal prerequisites for this definitive palliation are normal ventricular function with normal atrioventricular valve function and free outflow via the ventricular outflow tract and the aorta as well as adequate pulmonary artery size with low mean pulmonary arterial pressure, low transpulmonary gradient and low pulmonary vascular resistance.[110, 111] Decisive for a successful Fontan operation are a low pulmonary vascular resistance and a low pulmonary artery pressure.[110]

Extracardiac conduit, intraatrial lateral and extracardiac tunnel are the surgical modifications which are essentially performed during TCPC. Via an extracardiac conduit, for instance a Gore-Tex tube or a valveless homograft, inferior vena cava blood is directed to the pulmonary arteries.[49, 116] As a bidirectional cavopulmonary anastomosis, the superior vena cava is anastomosed to the right pulmonary artery (Figure 17).[110] The intraatrial lateral tunnel is constructed by placing a possibly fenestrated patch between the junction of the inferior vena cava and the superior vena cava stump.[110] The inferior vena cava blood can flow directly into the pulmonary artery through this channel.[49, 110] The extracardiac tunnel is placed on the exterior wall of the right atrium from the inferior vena cava to the pulmonary artery.[110] In addition, a fenestration can be implemented that represents a surgical creation of an ASD in the atrial patch, conduit or baffle to embodying an escape valve enabling a right-to-left

shunt.[117] It reduces pressure in the systemic venous circuit and ensures a sufficient preload of the systemic ventricle.[112] Nevertheless, higher cardiac output results in lower oxygen saturation.[110]

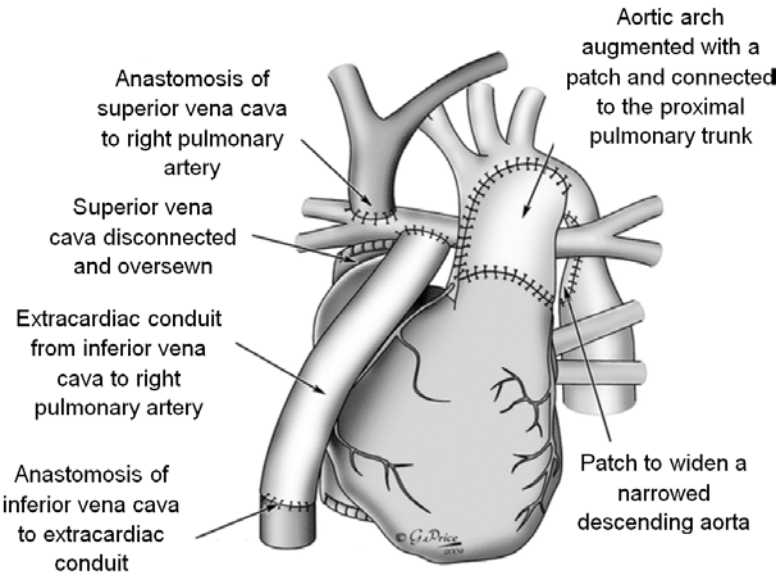

Figure 17: Total cavopulmonary connection
Total cavopulmonary connection with extracardiac conduit. Modified from[118]

3.1.4.2.4 Fontan surgery and its modifications

The initial aim of the original Fontan surgery was to create a circulatory system in which the systemic and pulmonary circulations are connected in series, driven by a single ventricle and a right atrium, substituting the right ventricle.[97, 115] This procedure included direct anastomosis of the right atrium to the main pulmonary artery resulting in systemic venous blood entering the pulmonary circulation, while bypassing the right ventricle.[49, 97] The right pulmonary artery was connected to the superior vena cava by a Glenn shunt, additionally superior vena cava–atrial junction was ligated.[97] To enable blood flow from the superior vena cava to the right pulmonary artery and from the inferior vena cava to the left pulmonary artery, connection between the right atrium or right atrial appendage and the left pulmonary artery was established using an aortic homograft or a conduit (Figure 18A).[97]

Shortly thereafter APA and AVA were performed. APA is based on the concept that the diastolic properties of the systemic ventricle represent the driving force of this system, acting as a suction pump.[119] Since the right atrium only functions as a pathway and not as a ventricular pump, these diastolic properties embody the only pump of the total right heart bypass system.[120] The procedure results in a total pulmonary ventricle bypass via APA, consisting of surgical sectioning of the pulmonary artery stem and closure of ASD by a

patch.[119] The right atrium was connected to the pulmonary artery with a homograft, with the patient's own pulmonary artery or without any valvular implant (Figure 18B).[119]

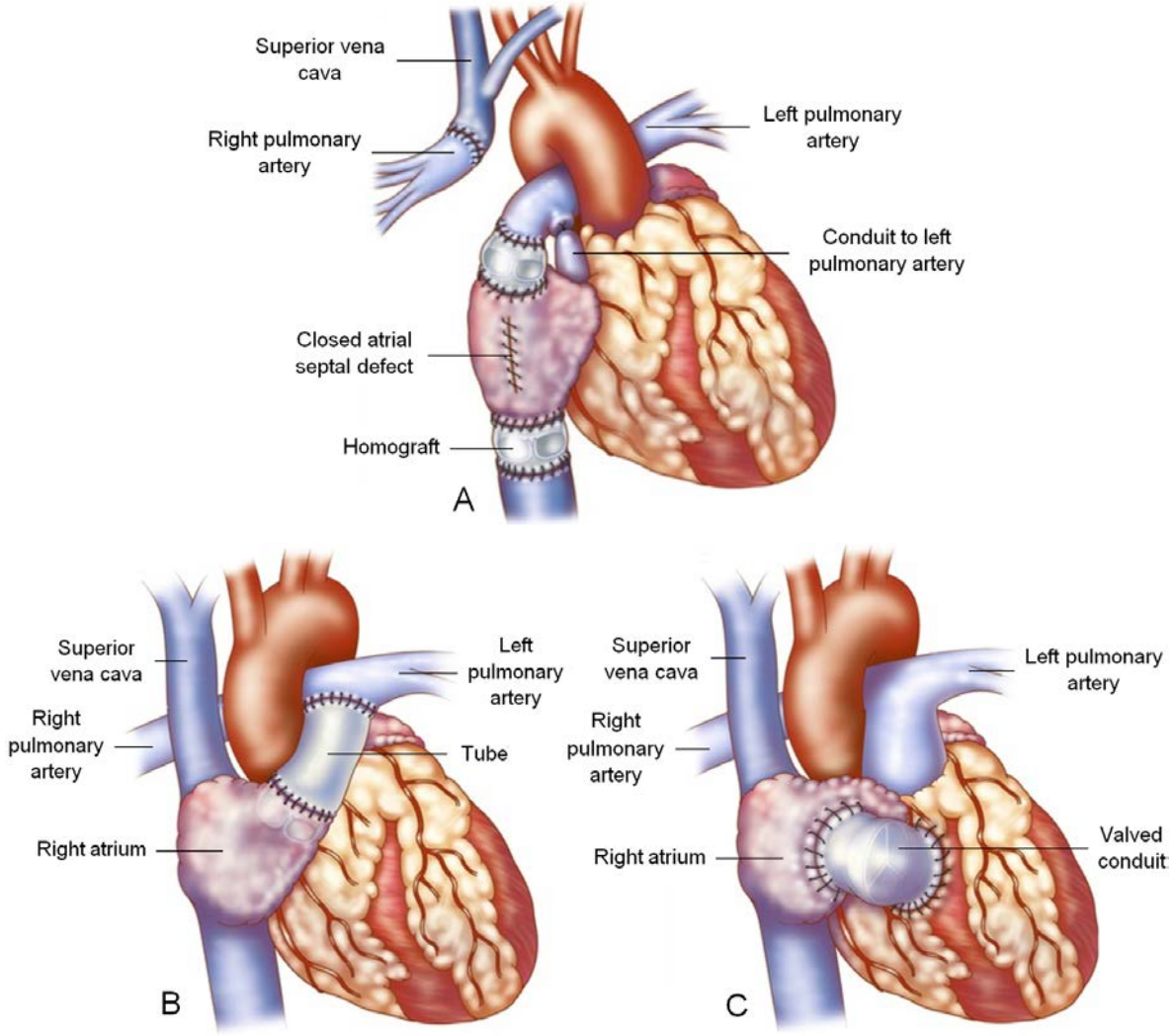

Figure 18: Original Fontan surgery and its modifications
A: Original Fontan surgery; **B**: Atriopulmonary anastomosis; **C**: Atrioventricular anastomosis. Modified from[121]

AVA results in a conjunction of the right atrium to the ventricle, implanting a conduit of entirely autologous material.[122] A pericardial patch was implanted connecting the right atrial appendage to the right ventricle.[123] After palliation, the lung valve is in its natural position and the right ventricle acts as a pumping chamber if it is not too hypoplastic (Figure 18C).[122] The assumption that the right atrium could act as a pulsatile chamber and thus improve pulmonary blood flow was disproved by the fact that the right atrium dilated and lost its contractile function.[120, 124] The dilation and loss of contractility led to turbulence and energy loss, which in turn reduced pulmonary blood flow.[112, 124] Consequently, procedures that created right atrial-pulmonary circuits were replaced by newer techniques. These newer techniques result in a more efficient cavopulmonary blood flow to the lungs by establishing a direct

communication between each vena cava and the pulmonary arteries, bypassing the right atrium and right ventricle.[112, 124]

3.1.4.2.5 Complications and long-term sequelae in operated patients

In a normal circulation the systemic circulation and the pulmonary circulation are connected in series and powered by a double chamber pump. In patients with Fontan circulation the systemic venous blood flows directly to the lungs without interposition of a pumping ventricle (Figure 19).[125]

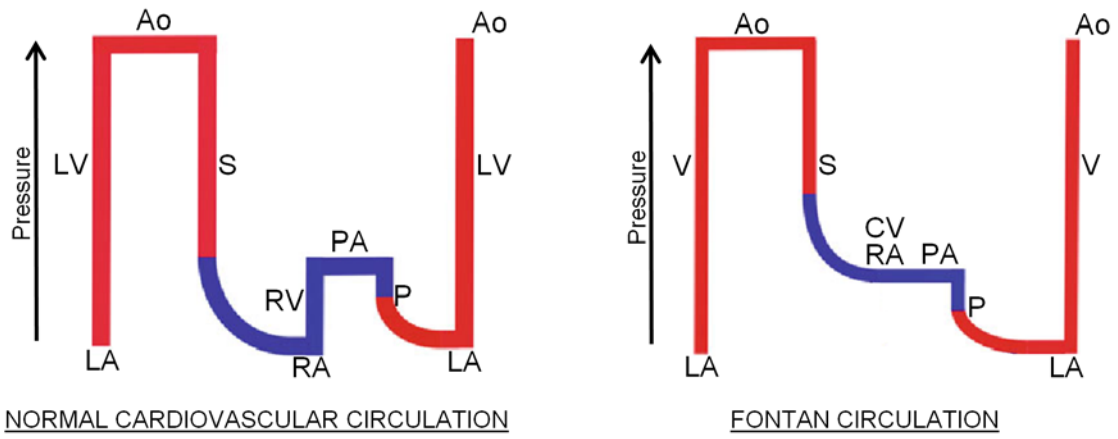

Figure 19: Schematic representation of the normal cardiovascular circulation and Fontan circulation
The pulmonary circulation (P) is connected in series with the systemic circulation (S). The right ventricle maintains a right atrial pressure lower than the left atrial pressure, and provides enough energy for the blood to pass through the pulmonary resistance. (Right) Fontan circulation: the systemic veins are connected to the pulmonary artery (PA), without a subpulmonary ventricle or systemic atrium. In the absence of a fenestration, there is no admixture of systemic and pulmonary venous blood, but the systemic venous pressures are markedly elevated. Ao: aorta; CV: caval veins; LA: left atrium; LV: left ventricle; PA: pulmonary artery; RA: right atrium; RV: right ventricle; V: single ventricle. Modified from[125]

Chronically preload-deprived ventricle, markedly altered pulmonary hemodynamics and chronic systemic venous hypertension are potential consequences of the lack of a subpulmonary ventricle, which could lead to a late Fontan failure.[50, 112] Regarding to this, atrial enlargement, a progressive decline in systemic ventricular function, pulmonary venous obstruction, atrioventricular valve regurgitation, a rise in pulmonary vascular resistance and the consequences of chronic systemic venous hypertension including hepatic congestion and dysfunction are important hemodynamic issues for survival of patients with Fontan circulation.[49, 110, 126] Additional negative predictors for survival are a right systemic ventricle, earlier Fontan modifications, chronotropic incompetence, arrhythmias, the presence of protein losing enteropathy and an accompanying heterotaxy syndrome.[32, 49, 50, 98-100] Veno-venous collateral vessels are common in patients with Fontan circulation and may lead to substantial

right-to-left shunts and cyanosis.[110, 112] Moreover, these patients suffer from dyspnea, fatigue and exercise intolerance.[50, 112, 127]

Even in clinically good Fontan circulation, there is an inadequate diastolic filling of the systemic ventricle due to the passive pulmonary flow.[110] Chronic preload depletion leads to diastolic and systolic dysfunction of the ventricle.[42, 112] This can result in impaired compliance, poor ventricular filling and ultimately low cardiac output.[42, 112] The latter can be caused or exacerbated by stenoses and valve insufficiencies. Since venous return in Fontan circulation is also strongly dependent on respiration, diaphragmatic paresis and scoliosis can contribute to additional impairment.[110] Any interference of pulmonary perfusion leads to excessive venous hypertension and reduced preload, which in turn can result in systemic ventricular dysfunction.[42, 128, 129] The consequence is a failure of the Fontan circulation.

3.1.5 Uncommon congenital deformities

Uncommon congenital heart malformations include various diagnoses and subgroups of CHD. Among others the Ebstein's anomaly, implicating a wide spectrum of anatomical and functional anomalies of tricuspid valve and right ventricle, and the Marfan syndrome, resulting in an autosomal dominant disorder of connective tissue encompassing cardiovascular, pulmonary, ocular, skin, skeletal and dura mater abnormalities, as well as CHD representing anomalous left coronary artery from the pulmonary artery, cardiomyopathies or channelopathies.[49, 50]

Due to their low prevalence, they are described as uncommon heart malformations in this thesis and will not be discussed in detail in the current dissertation. These heart defects were assigned to the miscellaneous group in Study II.

3.1.6 Classification according to severity

Diagnoses of CHD can be categorized into mild, moderate and complex according to the severity of their lesions. This chapter explains how CHD were classified by severity in Study II. Patients with a complex heart defect, such as patients with UVH, TGA or tricuspid atresia, have an incidence of 1.5 in 1,000 live births (Table 1).[130] The survival rate is expected to increase over the next decade due to improved surgical techniques.[12] The approximate numbers of survivors in this group were derived based on the documented incidence of live births for complex CHD and by extrapolating the probable survival rates for early through

recent years.[130] Patients who were born with moderate complexity or simpler lesions, but acquired complications have a prevalence of 2.5 in 1,000 live births.[130] Patients with moderate severity have malformations like ASD causing right heart dilation or VSD with valve lesions, but also ToF and supravalvular or subvalvular AS (Table 2).[12] Specifying the absolute prevalence of simple lesions is not quite as obvious (Table 3). For example, VSD will have closed until adulthood and these patients will no longer be considered to have CHD, while PDA will remain patent or need to be closed and are therefore defined as moderate CHD.[12] Taking these assumptions into account, the prevalence of these lesions is derived as 2.2 in 1,000 live births.[130] However, these statistics may be underestimated as they are based on the frequency of CHD presentations in infancy and childhood and at least 10% of cases seen in an ACHD clinic are not diagnosed until adulthood, for example ccTGA, Ebstein's anomaly and secundum ASD.[12, 130]

Compared to the healthy population and patients with mild severity, patients with more complex CHD are more vulnerable to additional acquired comorbidities affecting both cardiac and medical care.[12] As majority of these adult patients has an increased risk of re-operation, complications and premature death, they should be regularly seen in ACHD centers and followed for life.[131] Patients with mild defects may also benefit from at least one review at such a center, although less than half of patients with mild defects, such as mild PS or small VSD, do not require regular follow-up in an ACHD center.[12] Modifications in expected disease patterns, such as new cardiac and hemodynamic problems and functions, can be enabled through definitive repair at an earlier age and improved surgical procedures. Accordingly, the profile of this patient population will change over the next decades due to increased survival of patients with more complex anomalies.[12]

Table 1: Types of adult patients with congenital heart disease of complex severity

Conduits, nonvalved or valved
Cyanotic congenital heart (all forms)
Double-outlet ventricle
Eisenmenger's syndrome
Fontan procedure
Mitral atresia
Single ventricle
Pulmonary atresia (all forms)
Pulmonary vascular obstructive diseases
Transposition of the great arteries
Tricuspid atresia
Truncus arteriosus / hemitruncus
Other abnormalities of atrioventricular or ventriculo-arterial connection

Modified from[12]

Table 2: Types of adult patients with congenital heart disease of moderate severity

Aorto-left ventricular fistulae
Anomalous pulmonary venous drainage, partial or total
Atrioventricular canal defects (complete or partial)
Coarctation of the aorta
Ebstein's anomaly
Infundibular right ventricular outflow obstruction of significance
Ostium primum atrial septal defect
Patent ductus arteriosus (not closed)
Pulmonary valve regurgitation (moderate to severe)
Pulmonic valve stenosis (moderate to severe)
Sinus of Valsalva fistula / aneurysm
Sinus venosus atrial septal defect
Subvalvar or supravalvar aortic stenosis
Tetralogy of Fallot
Ventricular septal defect with
Absent valve or valves
Aortic regurgitation
Coarctation of the aorta
Mitral disease
Right ventricular outflow tract obstruction
Straddling tricuspid / mitral valve
Subaortic stenosis

Modified from[12]

Table 3: Types of adult patients with congenital heart disease of simple severity

Native disease
Isolated congenital aortic valve disease
Isolated congenital mitral valve disease
Isolated patent foramen ovale or small atrial septal defect
Isolated small ventricular septal defect (no associated lesions)
Mild pulmonic stenosis
Repaired conditions
Previously ligated or occluded ductus arteriosus
Repaired secundum or sinus venosus atrial septal defect without residua
Repaired ventricular septal defect without residua

Modified from[12]

3.2 Exercise training

This chapter aims to provide an overview of the aspects to be considered in sports recommendations in addition to the hemodynamic function in patients with CHD. Furthermore, it explains elementary components of the training theory, sports scientific definitions, training contents and prerequisites as well as training principles and components of fitness, which are decisive for a goal-oriented and successful exercise training implementation.

Sports medicine is indispensable for training theory nowadays. The motivation to maintain or improve good physical performance varies considerably depending on scientific or practical sports disciplines such as cardiology or orthopaedics.[132] Physical training and sport can counteract the inevitable lack of muscular strain in today's technological world and facilitate

the accomplishment of everyday tasks.[132] According to medical definition, sport is considered muscular strain with the goal of outstanding personal performance or competitive character.[132] The sum of all activities leading to a planned increase in physical performance, such as muscular strain, diet and lifestyle, is called training.[132] It can also be applied physically, motorically, cognitively, psychologically and affectively in various fields.[132]

Any bodily movements that lead to additional energy consumption beyond basal metabolic rate are referred to as physical activity.[133] Physical training represents a section of physical activity. Planned, structured, repeated and targeted, it results in an improvement in physical fitness and essentially comprises the technical-coordinative, cognitive-tactical, physical-energetic and psychosocial components differing in terms of objectives.[133, 134] In the current dissertation, exercise training is regarded as a systematic repetition of targeted supra-threshold muscle tensions, which aim to increase performance being accompanied by functional and morphological adjustments.[134] Exercise training is a complex action process involving for instance a targeted and planned development of exercise capacity.[134] A targeted development means that all actions are aimed at achieving the desired goal. A planned course of training includes the definition of training goals, contents and methods in advance as well as a control of the implementation and a verification of the effectiveness on the basis of performance controls.[134]

Adaptability represents the basic prerequisite for the entire training process.[132] The extent and type of strain affect the performance and structure of organ systems and individual organs, as living beings can adapt to different stimuli.[135] In the sense of stimulus processing physical activity results in an improvement of exercise capacity. These adjustment processes, which represent protective mechanisms for improved load tolerance, are due to disturbances in the balance of internal metabolic processes and are triggered by supra-threshold stimuli.[132, 135] The impact of training consists continuously of degradation processes, which are triggered by exercise, and reconstruction processes during the recovery phase, which result in super compensation, equivalent to an increase in performance reserves.[132, 135]

3.2.1 Training principles

Methodical principles for planning, controlling and designing exercise training have a high relevance, since a multitude of different regularities strongly influence an effective training design.[134] The methodical action orientation can be improved by the principles of exercise training, which have to be considered and applied in a complex way due to their unsolvable

connections.[134] Training principles that relate to all aspects and tasks of the training and determine the content as well as the organization and methods are valid for action orientations for the training.[134] The four different categories of basic principles of exercise training, which require biological adjustment processes, are divided into principles of strain, principles of cyclisation, principles of specialization and principles of proportion. Principles of strain indicate the need for a stimulus to exceed a certain threshold in order to cause adaptation.[134, 135] Furthermore, there should be a progressive increase in exercise and varying exertion to provide new stimuli for improved response.[134] Principles of cyclisation to ensure adaptation include optimal configuration of load and recovery.[134, 135] In this respect, stimulation should occur repeatedly and continuously.[134] Principles of specialization for controlling the adaptation into the specific direction consider, for instance, age-related and individual aspects of the athlete as well as the regulatory interactions.[134, 135] Principles of proportion to the development of the performance prerequisite address the optimal relationship between general and specific training and the development of the performance components.[134, 135] Not solely the consideration of the principles, but also the long-term planning, the planned organization and the evaluation of the training are important for the effectiveness of the training process.[134] Each training session, which is the smallest unit within the overall training process, should always consist of a preparatory part, a main part and a final part.[134]

3.2.2 Components of fitness

Since quantitatively and qualitatively different loads lead to different reactions, a clear differentiation of the components of fitness is necessary. They are divided into coordination, flexibility, strength, speed and endurance (Figure 20).[134, 135]

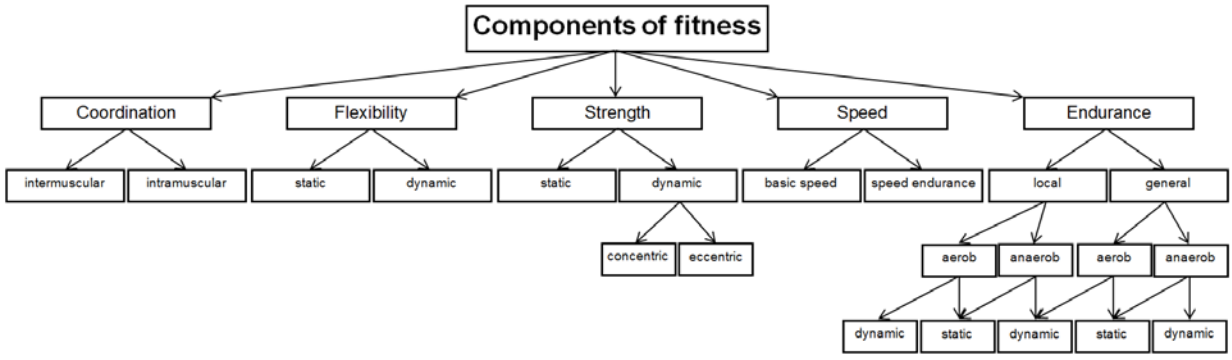

Figure 20: Basic scheme of components of fitness

Modified from[132]

Coordination represents the interaction of skeletal muscles and central nerves within a specific movement sequence.[132, 134, 135] Coordination gains in importance with the complexity of a sport specific movement. A higher quality of coordination is associated with a more precise achievement of the movement goal.[132] Arbitrarily possible range of motion in one or more joints describes flexibility.[132, 134, 135] Factors limiting performance are the extent of muscle mass, joint structure, stretching ability of the muscle, tendons and ligaments as well as the joint capsules and skin.[132] Strength, which can be subdivided into static or dynamic, includes the transformation of a state of rest or movement.[132, 134] The tension that a muscle group or a single muscle exerts arbitrarily against a fixed resistance in a certain position is termed static force.[132] However, dynamic force describes the mass that can be moved arbitrarily within a specific motion sequence.[132] The result of the impact of a force on a mass is called speed, while the related time to distance covered represents the magnitude.[132] Speed represents the ability to perform movement actions in a minimum period of time under given conditions.[134] In contrast, endurance represents the ability to maintain a given performance for as long as possible.[132, 134, 135] It is identical to fatigue resistance and can be further divided into morphological, physical and chemical aspects as well as local and global muscle endurance, aerobic and anaerobic energy supply and dynamic and static work.[132, 134, 135] These five components of fitness are interrelated, resulting in skills such as strength endurance and speed strength.[134] Additionally, different sports require different components at varying rates. For instance, endurance is particularly important from a preventive medical point of view for patients with cardiovascular diseases and patients with CHD.[19, 136, 137] Since skeletal muscles are not continuously active during exercise, they are supplied with anaerobic-alactacid, anaerobic-lactacid and aerobic-lactacid energy.[134] The heart muscle, by contrast, is almost exclusively dependent on aerobic energy production as it is constantly active.[134] It has a significantly higher number of mitochondria compared to the skeletal muscles.[134] Endurance training increases stroke volume and the related endurance capacity, which is associated with increased aerobic capacity, improved fatigue resistance and improved oxygen uptake.[134] Under normal circumstances, the lung volume respectively the diffusion capacity is not limiting for endurance exercises.[134] However, endurance training can cause adaptation, which is associated with greater lung volume, activity hypertrophy of the respiratory muscles and economization of respiratory function.[134] The inspiratory musculature can be performance limiting due to fatigue at maximum loads.[134]

3.2.3 Exercise capacity

Physical activity and exercise improve physical fitness, which is described as a combination of muscle strength, coordination, flexibility and cardiorespiratory fitness.[133] In addition, pulmonary, metabolic, orthopedic, genetic, and cardio-circulatory parameters influence the extent of training effects.[133] One partial aspect of physical fitness is cardiorespiratory fitness. It is determined by the maximum cardio-circulatory capacity and corresponds to the maximum capacity of oxygen transport from inhaled air to mitochondrial energy supply.[133] Exercise capacity, which represents the maximum possible physical performance of a person, is assessed by means of the peak oxygen uptake ($\dot{V}O_2$peak).[133, 134] Cardiopulmonary exercise tests (CPET) constitute the gold standard for the evaluation of cardiorespiratory fitness.[138] Individual performance capability and willingness to perform significantly determine exercise capacity.[132] Furthermore, the initial capacity, that is the physical condition and as appropriate the clinical condition, the frequency and intensity of the training determine the magnitude of exercise capacity.[139] However, exercise capacity and cardiovascular risk factors such as obesity, dyslipidemia, hypertension and type 2 diabetes mellitus can be affected positively by regular long-term physical training, in particular aerobic endurance training.[133, 140-142] Dynamic strength training as strength endurance and muscle building training also confirm positive effects regarding physical performance, muscular strength, bone density and cardiovascular risk factors.[143-146] Furthermore, study results indicate that high exercise capacity is associated with lower morbidity and mortality.[19, 30-33] Thus, the aims of secondary prevention are the improvement of physical resilience, which is associated with a favourable influence on the course and prognosis of disease and results in an improvement of cardiovascular morbidity and mortality as well as quality of life.[133, 139, 147, 148]

3.3 Heart rate variability

HRV is defined as the variability of the time between two adjacent heartbeats and represents a non-invasive measure quantifying activities of parasympathetic and sympathetic branches, reflecting spontaneous changes of the ANS (Figure 21).[149-151] Both pathways have an immediate influence on the sinus node, which manifests HRV by regulating the heart rhythm.[152] The sympathetic and the parasympathetic pathway represent two antagonistic functional subsystems of the ANS and adapt the organism to the changing environmental conditions.[153] The functioning of almost all organs is completely controlled by both branches, while the respective situation is decisive for the level of their respective activity.[153]

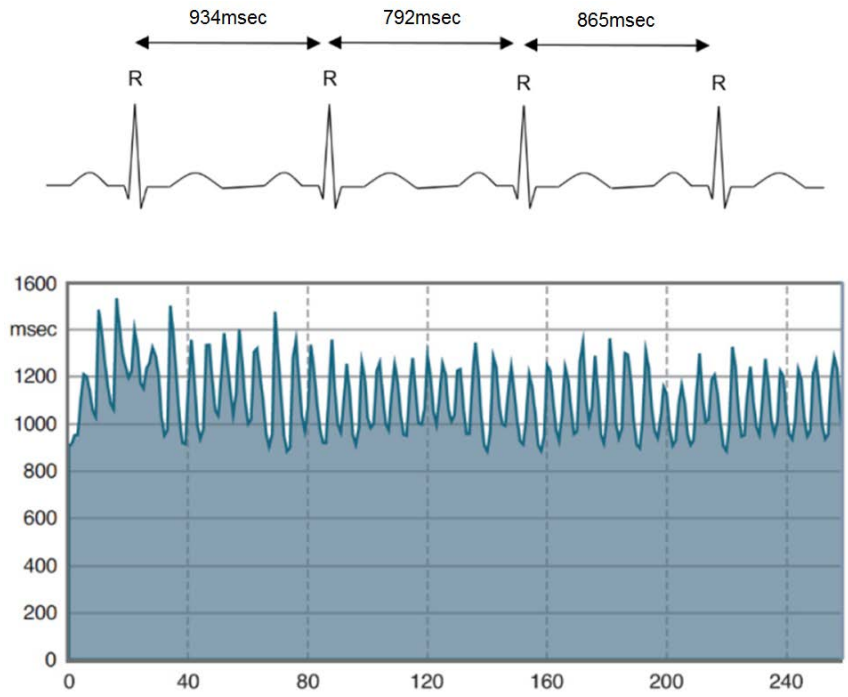

Figure 21: Rhythmogram with 260 recorded heartbeats
msec: milliseconds

3.3.1 Physiological basis of heart rate variability

Under resting conditions, the heart rate exhibits significant variability (Figure 22). When the organism is exposed to stress, an adaptation reaction of the heart follows, decreasing the range of variation between contractions.[153, 154] These fluctuations, for which the R-wave in the ECG is the reference point, are indispensable as the organism is permanently exposed to external and internal stimuli.[155, 156] Excitement, fear, joy and exercise activity increase the activity of the sympathetic nervous system, which adapts the necessary organs and systems, such as the cardiovascular system, the respiratory system and the working muscles, for the exertion through improved blood supply (Figure 22A).[153, 157, 158] While a stronger activity of the sympathetic nervous system adjusts the organism to the respective loads of a situation, the parasympathetic activity, which predominates at rest, decreases simultaneously.[156, 159] When the sympathetic nervous system is stimulated, the transmitter noradrenalin is secreted and binds to β-receptors of the pacemaker-competent sinus node cells.[160] As a result, the discharge frequency of the autonomous sinus node cells increases and the heart rate rises.[156] Following exertion, recovery phase begins and the parasympathetic activity increases, while the activity of the sympathetic nervous system decreases (Figure 22B).[159] The bodily functions working during exertion diminish and the organs and systems restoring the balance of the organism regain their activity. If the parasympathetic nerve is stimulated, the transmitter acetylcholine is released.[156] The binding of acetylcholine to the receptors of the sinus node cells results in a

reduction of the increase of the diastolic action potential, which in turn leads to a decrease in heart rate.[156, 161] While the parasympathetic nervous system can cause changes in the range of milliseconds, since cholinesterase causes acetylcholine to rapidly degrade in the synaptic cleft, the sympathetic nervous system can only generate effects in the range of seconds. Fluctuations from one heartbeat to the following are exclusively caused by parasympathetic activity.[159, 162]

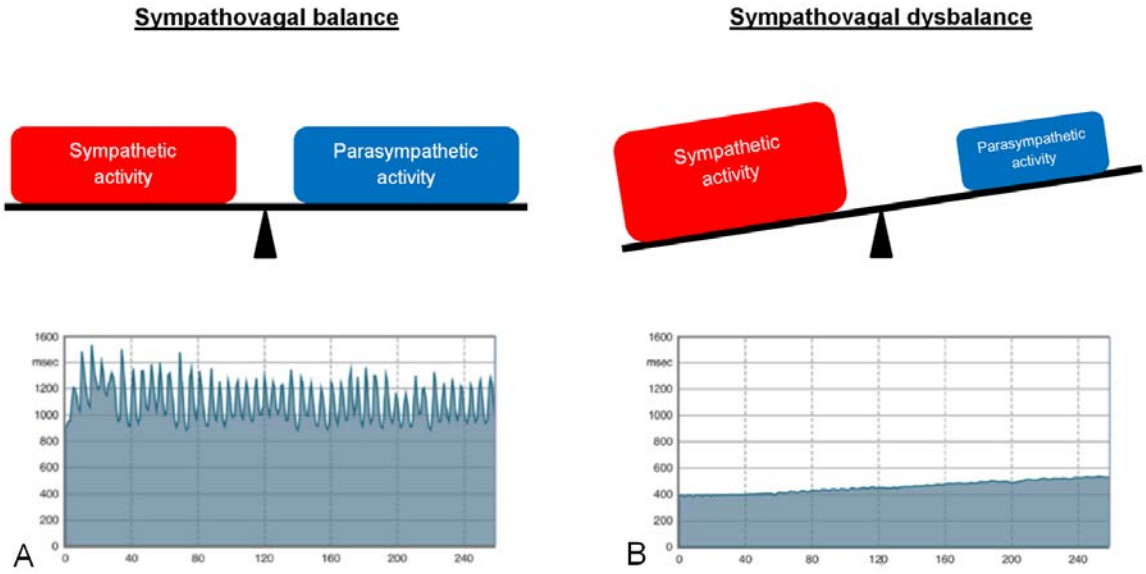

Figure 22: Comparison of sympathovagal balance and dysbalance
A: Sympathovagal balance at rest; **B**: Sympathovagal dysbalance after physical activity
msec: milliseconds

The two pathways cannot be considered independently of each other, as many situations require complementary interaction.[156] HRV is manifested by a combination of tachycardic and bradycardic phases, resulting from the constant vegetative modulation of the sinus node.[152, 156] As the heart exhibits higher HRV under resting conditions, it reacts more directly and flexible to internal and external influences and the organism adapts better to changing environmental conditions.[154] A decreased HRV at rest describes a limited ability to adapt caused by an imbalance in the vegetative nervous system.[154, 163] A large number of studies has shown that a reduction in HRV is associated with an increased risk of mortality and morbidity.[37, 164, 165] Influencing factors of HRV are age, gender, physical condition, physical work load, muscle activity, stress, body position, time of day, food intake such as caffeine and alcohol, temperature, medication and nicotine, while age, inversely correlated with HRV, and average heart rate represent the strongest determinants.[163, 166-170] Breathing in the sense of respiratory sinus arrhythmia has a further influence on the variability between heartbeats.[171, 172] Physical activity and cardiovascular fitness counteract a reduction in HRV at rest, since increased parasympathetic and reduced sympathetic activities go along with better exercise

capacity.[28, 34, 173] Regular physical activity results in an increase in parasympathetic activity and in a decrease in sympathetic activity and resting heart rate in the sense of a significant rise in overall variability, which is accompanied by improved regulation of the ANS.[173, 174]

3.3.2 Analyses and parameters of heart rate variability

HRV can be evaluated in several ways. The most common are the frequency domain method and the time domain method. In frequency-based analyses, the recorded overall signal is fragmented into oscillations by spectral analysis and assigned to different frequencies. These frequency ranges result in characteristic components such as high frequency, low frequency and very low frequency components by short-term recordings.[156] Higher frequencies are attributed to parasympathetic activity, while lower frequencies are related to sympathetic activity. The high frequency component, for instance, reflects the parasympathetic activity and is comparable to the parameter that represents the parasympathetic activity in time-based methods.[156] Since this dissertation exclusively employed the time-based analyses, the frequency domain method is not discussed in detail.

The time domain method is based on the assumption that the sequence of the heartbeat is random.[153] Dispersion behavior around the mean value of the recorded HRV signal is taken into account. The absolute interval duration between two adjacent regular QRS complexes serves as the basis for qualitative time-based analyses.[156] During the measurements, four time-based parameters and one non-linear parameter were recorded. Since only one parameter representing parasympathetic activity was considered in Study II, the remaining parameters are not examined in more detail below.

One of the most frequently used parameters of the time domain method is the RMSSD which embodies the square root of the mean of the sum of the squares of differences between adjacent normal-to-normal (NN) intervals. This parameter is calculated from the square root of the squared mean value of the sum of all differences between adjacent RR intervals.[156] The RMSSD is considered to be a selective measure of parasympathetic activity due to high frequency oscillations.[156] A high RMSSD is due to increased parasympathetic activity, while a lower RMSSD is detectable under exertion.[156] The latter is an indication of reduced activity of the parasympathetic nervous system and increased sympathetic activity.[158] Norm values for healthy adults are at rest between 24.0 - 92.0ms.[175]

The parameter SDNN defines the overall variability by measuring the standard deviation of all NN intervals and represents the mean value of the standard deviation of all RR intervals.[156]

High SDNN values are associated with a good overall variability and are attributable to a well-established interaction of the vegetative functional systems and a good adaptability of the ANS.[158] The heart rate is defined as the number of contractions per minute and is influenced by both pathways of the ANS by affecting intrinsic activity of the sinus node.[156] The stress index (SI) is calculated from the quotient of the number of most frequently occurring time intervals between adjacent RR intervals and the difference between the largest and smallest RR interval recorded during measurements. An increase may be due to physical or psychological stress or organic pathologies and is caused by enhanced sympathetic activity.[153] The parameter α1 is captured using a non-linear method. This parameter of the detrended fluctuation analysis reflects the quality of regulation in short-term measurements and consequently represents not only the temporal changes in HRV.[176]

3.4 Lung function

3.4.1 Anatomy and physiology of the respiratory system

The lung is composed of the right and left lung that almost fill the thorax. The trachea is divided into two main bronchial tubes, which continue to branch out and finally form the alveoli, enabling gas exchange.[135] The lung tissue is elastic and functionally fused with the thoracic wall resulting in a depression in the pleural cavity which is essential for respiration.[135]

Breathing is divided into oxidation of nutrients into the cell and ventilation, describing the gas exchange.[135] The alveolar membrane, representing the interface between the lungs and the circulatory system, separates two active transport systems from each other, which are connected by diffusion.[135] Oxygen (O_2) enters the blood through diffusion from the alveoli, while the carbon dioxide (CO_2) from the blood enters the alveoli and is removed with the exhaled air.[135] On the basis of different pressures the gas transport is carried out in the lungs. Gas transport during expiration is kind of passive, as the pressure in the lungs is higher than the atmospheric pressure.[135] In contrast, the pleural pressure for inspiration must become negative compared to the atmospheric pressure to inflate the lungs, which is caused by the widening of the thorax by diaphragmatic or thoracic breathing.[135]

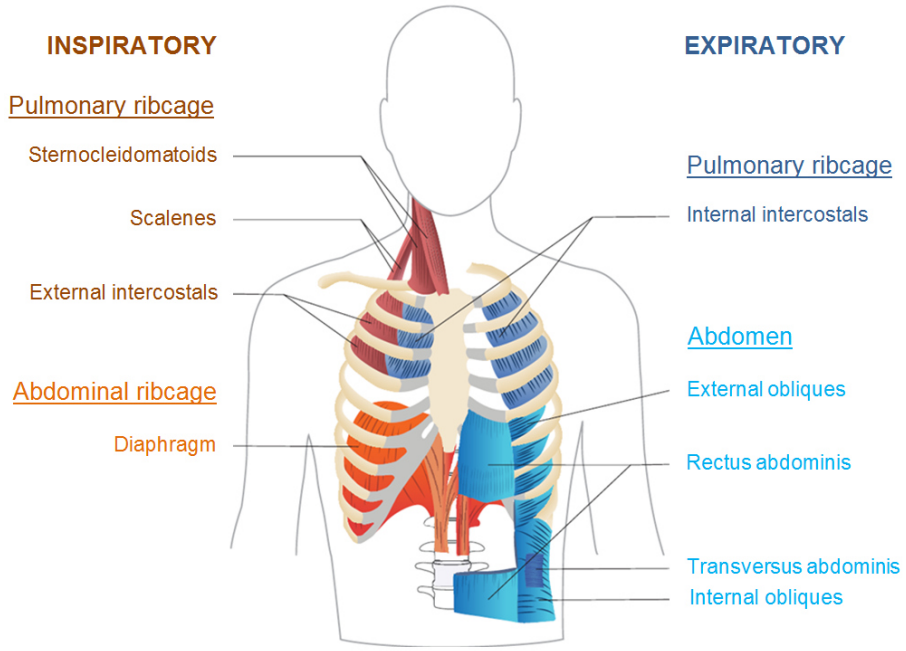

Figure 23: Inspiratory and expiratory muscles of respiration
Modified from[177]

The diaphragm, the intercostal and accessory muscles and the muscles of the abdomen represent the three groups of the respiratory muscles and have both inspiratory and expiratory functions (Figure 23).[178] During contraction of the diaphragm the abdominal viscera is pressed downwards, the abdominal wall is moved outwards and the abdominal pressure is increased.[178] The intercostal muscles comprise the internal and external intercostals. The accessory muscles include the scalenes, the sternocleidomastoids and the trapezoids.[178] The external intercostal and the accessory muscles are responsible for increasing the anterior-posterior diameter of the thorax and primarily serve an inspiratory function.[178] In the upper few intercostal spaces during quiet breathing inspiratory activity can be observed in the external intercostals. With increased ventilation the lower intercostals become active and with high levels of inspiratory activity, the accessory muscles and other back muscles supporting the chest cage are recruited.[178] Rectus abdominis, transverse abdominis as well as external and internal obliques belong to the abdominal respiratory muscles, which are commonly regarded as expiratory muscles reinforcing the passive recoil of the lungs, in particular during deep and forceful breathing.[178] Since the contraction of the abdominal muscles tends to lengthen the diaphragm and reduce its radius of curvature, it leads to higher tension and greater transdiaphragmatic pressure at a certain tension.[178] Therefore, abdominal muscles are also crucial for inspiration. In the upright posture and especially during exercise an improved diaphragm's mechanical function is important.[178] During diaphragmatic breathing, the cavity in the chest is widened by flattening the diaphragm due to its contraction.[135] During thoracic

breathing, the rib cage is raised through the contraction of the intercostal muscles and the scalenes.[135] The process of inspiration which is achieved by the active expansion of the thorax takes place actively. Exhalation which involves a narrowing of the thorax is predominantly passive. During exhalation, the raised rib cage is pulled downwards by gravity.[135] The muscles and lungs are stretched during inspiration. Due to reset forces, the stretched abdominal muscles pull the diaphragm upwards after relaxation and the external intercostal muscles pull the thoracic wall inwards again.[135] Furthermore, during exhalation, the diaphragm is pushed upwards by active contraction of the abdominal muscles and the rib cage is pulled downwards by the contraction of the internal intercostal muscles.[135]

3.4.2 Lung capacities and volumes

The measurement of lung volumes plays a decisive role in sports medicine with regard to the great relevance of oxygen uptake for energy supply.[30, 127] Additionally, spirometry is invaluable as a screening test for general respiratory health.[179] Spirometry is defined as the measurement of dynamic and static lung function parameters and respiratory flows and is performed by arbitrary and maximum breathing maneuvers or continuously to the measurement of ventilation (Figure 24).[180] It represents a non-invasive measurement of lung volumes and flows, and is suitable for the diagnosis of obstructive and restrictive ventilatory patterns.[180] A distinction is made between static and dynamic lung function parameters. While the measurements of static lung volumes do not depend on the time sequence of the spirogram, the measurements of the dynamic lung function parameters depend on the time sequence and can be displayed in the flow-volume curve.[180] The vital capacity represents the difference in volume of air that can be measured via a breathing tube inserted in the subject's mouth between the position of complete expiration and the position of full inspiration.[180] The inspiration is performed until the total lung capacity is reached and the expiration until the residual volume is reached. The vital capacity is determined in Germany in the form of the inspiratory vital capacity by initially exhaling slowly to the residual volume and then inhaling rapidly, but not forcibly. Inhalation is executed up to total lung capacity.[180] In contrast, expiratory vital capacity is measured during slow expiration from the level of total lung capacity with increasing effort at the end of expiration.[180] Between the inspiratory vital capacity and expiratory vital capacity there is no systematic difference in healthy people. If expiration is maximally forced after initial slow expiration and rapid maximal inspiration, the measured vital capacity is defined as forced expiratory vital capacity (FVC).[179-181] In order to achieve forced expiration, inhalation is performed rapidly up to the total lung capacity and

immediately followed by exhalation over several seconds with maximum effort up to the residual volume.[180] Muscle strength should be increased suddenly and not gradually. Forced expiratory volume in the first second (FEV_1) can also be captured during this manoeuvre. FEV_1 and FEV_1/FVC represent parameters for the detection of forced expiration.[180] FEV_1 is defined as the absolute maximal volume that can be exhaled by forced expiration within the first second after full inspiration.[179, 181] The second parameter is the Tiffeneau index, describing the relative FEV_1 and is presented in relation to the FVC.[180]

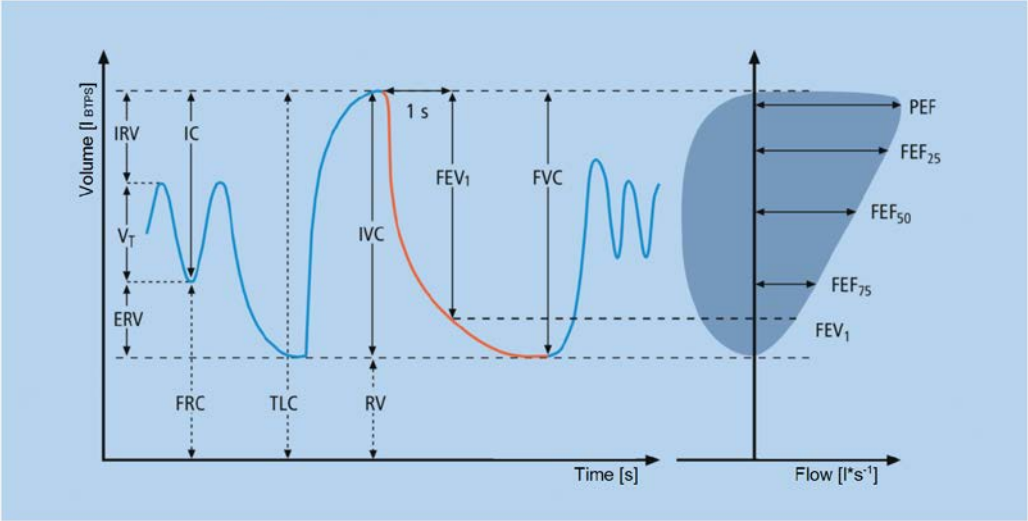

Figure 24: Static and dynamic lung function parameters and maximum expiratory flows
BTPS: body temperature, pressure, water vapor saturated (corresponding to conditions within the lungs); ERV: expiratory reserve volume; FEF: forced expiratory flow (25%, 50% or 75%); FEV_1: forced expiratory volume in the first second; FRC: functional residual capacity; FVC: forced vital capacity; IC: inspiratory capacity; IRV: inspiratory reserve volume; IVC: inspiratory vital capacity; l: liter; PEF: peak expiratory flow; RV: residual volume; s: second; TLC: total lung capacity; V_T: tidal volume. Modified from[180]

With advancing age, volumes and capacities for instance residual volume and functional residual capacity increase, while FVC and FEV_1 decrease due to loss of expiratory muscle strength, reduced compliance of the chest wall and the growing tendency of the smaller airways to close during forced expiration.[182, 183] Total lung capacity, vital capacity, residual volume, FVC and FEV_1 are proportional to body size.[184] Consequently, a greater decrease in lung volume is associated with a larger body size and increasing age. Reference values for lung function factor in the most important anthropometric factors such as age, height, weight and gender.[184] Loss of alveolar surface and diminished blood volume which are associated with age lead to a reduced gas exchange.[185] A larger number of bronchi, greater alveolar surface area and a wider airway caliber could be demonstrated in men compared to women.[186] Due to an increase in the volume of the chest cavity, highest long volumes can be achieved in an upright position.[187] Additional factors such as physical position, social and healthcare considerations, physical parameters, genetic factors, lifestyle and diseases are taken into

account for interpretation of lung function.[188-190] The latter includes among others, diabetes, hormone or muscle disorders. Patients with CHD show respiratory muscle weakness and especially Fontan patients suffer additionally from restricted chest walls and diaphragmatic palsies.[43, 191] Study results indicate that impairments in respiratory musculature strength are associated with a reduction in exercise capacity.[44, 45]

3.4.3 Ventilatory defects

There are different types of ventilatory defects, such as obstructive and restrictive abnormalities, which can be detected and quantified using spirometry. Ventilatory obstruction is defined as a disproportionate decrease in the maximum airflow from the lung in relation to the maximum volume which can be expelled from the lung.[192] The reduction of the maximum expiratory airflows is characteristic of this abnormality and is represented as a concave shape in the flow-volume curve (Figure 25A).[192] Due to its airway narrowing during expiration, it implicates a reduced FEV_1/FVC ratio of the predicted value.[180, 192] The international GOLD recommendations specify obstructive abnormalities by an age-independent decrease of the postbronchodilatory FEV_1/FVC ratio below 70%.[193] Severity of ventilatory obstruction is expressed by the impairment of FEV_1 as percentage predicted in clinical assessment. Time segments of the spirogram, such as FEV_1, are typically decreased disproportionately to reduction of vital capacity when the airway disease is more progressive and / or more central airways are affected.[192]

Ventilatory restriction is defined as a limitation of normal lung extension or lack of lung parenchyma.[180] It is characterized by a disproportionate reduction in total lung capacity and is represented as a convex shape in the flow-volume curve (Figure 25B).[180, 192] Vital capacity can be reduced by an increase in residual volume caused by hyperinflation without any restriction.[180] Consequently, a reduced total lung capacity cannot be detected by spirometry and a reduced vital capacity cannot provide evidence of a ventilatory restriction.[194, 195] However, hyperinflation associated with an increase in residual volume is unlikely if FEV_1/FVC ratio is normal or increased.[180] Reduced vital capacity indicates restrictive abnormality, which are characterized as a decrease of the FVC below 80% predicted.[192] Severity of ventilatory restriction is screened by the impairment of vital capacity either by inspiratory vital capacity or during forced expiration by FVC.[180] However, it has to be confirmed with a reduced total lung capacity, as end-stage obstructive lung disease causes an

increase in the residual volume of the lung and limitations in vital capacity.[180] Despite total lung capacity is not affected.

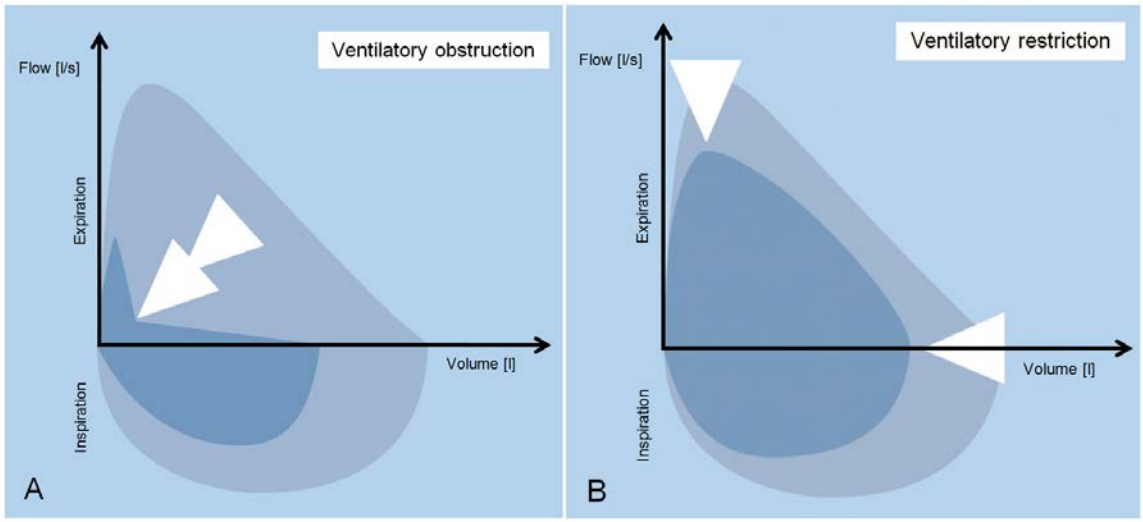

Figure 25: Ventilatory defects
A: Ventilatory obstruction; **B**: Ventilatory restriction
l: liter; s: second. Modified from[180]

4 Study design

Study I is a review and not included in this chapter.

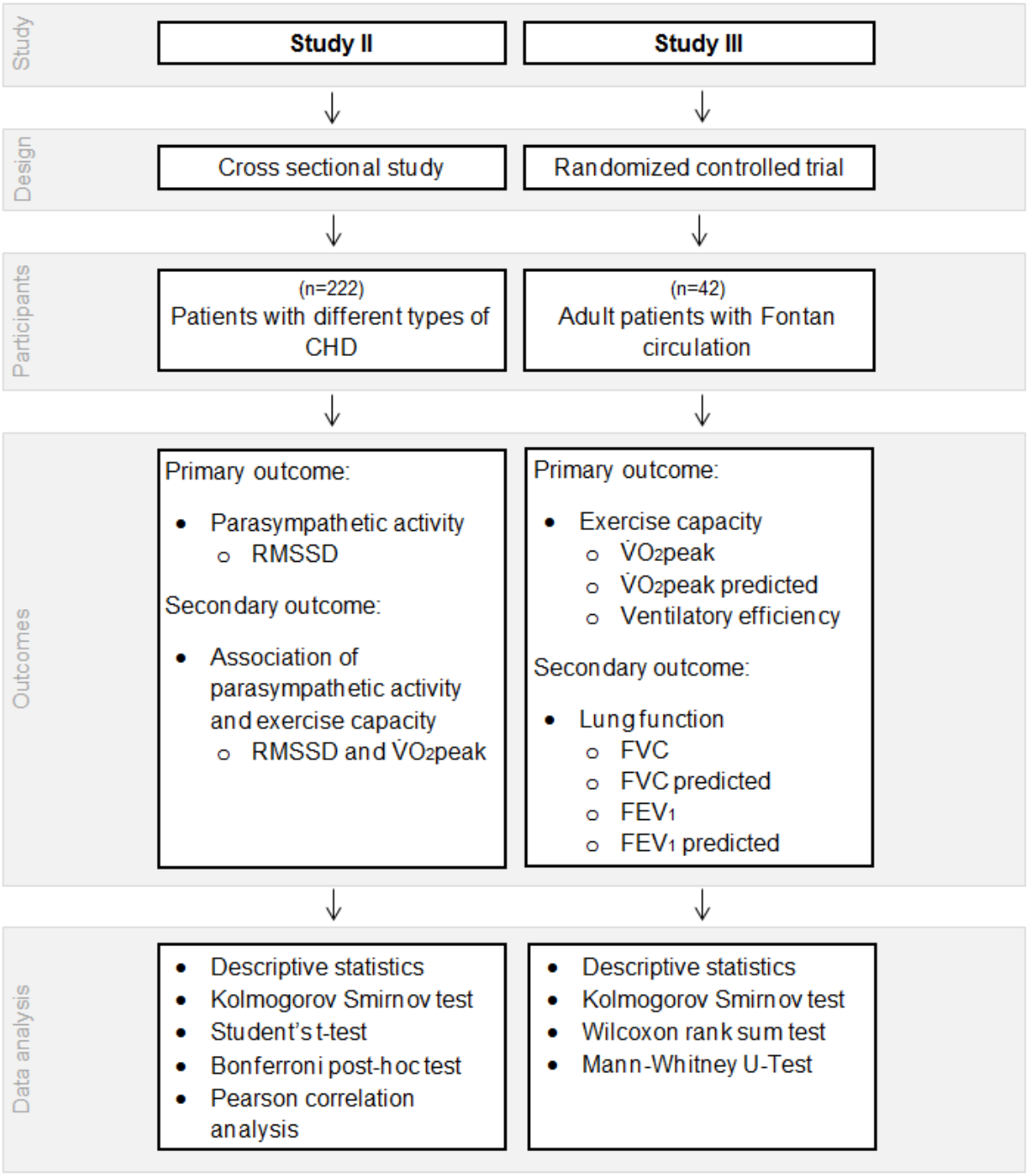

Figure 26: Study design

CHD: congenital heart disease; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; RMSSD: root mean square of successive differences; $\dot{V}O_2$peak: oxygen uptake at peak exercise

5 Publications

5.1 What Kind of Leisure Sports is Suitable for Adults with Congenital Heart Diseases?

Authors: Celina Fritz, Alfred Hager

First Author: Celina Fritz

Current Status: Published; Deutsche Zeitschrift für Sportmedizin

Individual contribution:

I was responsible for literature research and writing the review. I represent the main author of this paper and was mainly responsible for the submission.

All actions were taken in consultation with Prof Dr. Alfred Hager who gave important input for revising and improving the quality of the manuscript. The topic was suggested by the journal.

Summary and main results:

Study I aims to encourage cardiologists to make suitable recommendations for adult patients with CHD regarding physical activity in accordance with recent guidelines, considering hemodynamic function, diagnostic findings, medication and patient's requests and expectations.

Exercise capacity is one of the most robust predictors of survival and health outcome, since a reduced exercise capacity is associated with a higher risk for hospitalization or death. Physical activity and sports participation improve exercise capacity and therefore cardiovascular and health benefits. Since patients with CHD show reduced exercise capacity in comparison to the healthy population, these patients would profit even more from physically active lifestyles, since improved exercise capacity reduces the risk of suffering from cardiovascular and chronic diseases.

In order to make a safe recommendation on physically active lifestyles residuals with a specific risk for adverse events during physical activity have to be identified by means of sport eligibility testing, consisting of medical history, physical examination, electrocardiography, echocardiography and CPET. Since sport eligibility is determined by the

patient's risk that acute cardiac problems may occur related to activity or develop in long-term with certain exercise, it is notably dependent on the results of recent examinations and less dependent on exercise capacity and the initial congenital heart disease. The precise knowledge of the heart disease, therapeutic steps and current cardiac situation including all residual findings are required for identification of the age-appropriate development of cardiopulmonary status, heart rhythm, exercise capacity as well as cardiac functionality and the hemodynamic significance of the residual findings, at rest and during exercise. The patient's exercise capacity and individual risk are not only determined by the initial congenital heart disease, but also its sequence of therapeutic interventions as well as the extent of the residual findings and the evaluation of the functions. Therefore, it is more reasonable to focus on the hemodynamic function and to consider the unique clinical status than solely focusing on the type of defect. Among others ventricular dysfunction, aortic abnormalities, syncope, cyanosis, pulmonary hypertension, arrhythmia, ion channel diseases, cardiomyopathy and medical drug treatment have to be considered in the recommendation of exercise training.

Exercise training needs to be planned, structured, repeated, targeted and also adjusted individually on the basis of a risk evaluation, taken into consideration the type and severity of the heart disease as well as the patient's characteristics like sex, age, previous physical inactivity and exercise experiences, preferences, skills, motivation and training goals. Individual training schedules should contain specifications about training frequency, exercise intensity, workout time, type of exercise and training, as well as training method and training goal. Especially in patients with CHD it is recommended to consider the dynamic or static performance, the degree of impact, the patient's individual exercise capacity as well as to start at low level and to increase the exercise intensity, training frequency and workout time slowly but steadily.

To reassess the sport recommendations annual follow-ups need to be conducted to consider recent diagnostic findings. Specific restrictions should only be addressed in case of medical issues and should be discussed individually with the patient. In general, most patients with CHD can join regular sport clubs with no risks and physical activity can be integrated in the patient's daily life.

Welcher Freizeitsport ist für Erwachsene mit angeborenem Herzfehler geeignet?

What kind of leisure sports is helpful for adults with congenital heart diseases?

Summary

Most patients with congenital heart diseases profit from physical activity and physical exercise training. Physical activity improves exercise capacity and, therefore, reduces the risk of suffering from cardiovascular and chronic diseases. Even patients with former congenital heart diseases have a reduced physical capacity compared to the healthy population despite no hemodynamic sequelae. They should be encouraged to do physical activities to improve quality of life and to prevent acquired cardiovascular disease. Nevertheless, in some patients precautions have to be taken and recommendations have to be made according the individual residual findings in order to minimize risks of cardiac events.

This article summarizes the recent sport recommendations for adults with congenital heart diseases in consideration of the diagnostic findings, medication and patient's requests and expectations. As sport eligibility notably correlates with the recent findings, it is more useful to focus on hemodynamic function than on the type of defect.

The majority of sport activities can be recommended for most patients. Fundamentally, annual medical surveillance needs to be conducted to reassess the sport recommendations considering recent diagnostic findings. Specific restrictions should only be addressed in case of medical issues. These restrictions should be discussed individually with the patient, taking any diagnostic findings and the patient's requests as well as their expectations into account.

Key Words: Congenital heart disease, Recommendation, Restriction, Residual findings

Zusammenfassung

Die Mehrzahl aller Patienten mit angeborenem Herzfehler profitieren von körperlicher Aktivität und gezieltem Training. Die körperliche Aktivität verbessert die Leistungsfähigkeit und damit die Lebensqualität sowie die soziale Einbindung in das Freizeit- und Berufsleben. Erwachsene mit angeborenem Herzfehler weisen trotz derselben hämodynamischen Situation, verglichen mit der gesunden Population, eine reduzierte physische Kapazität auf. Nur selten müssen Vorsichtsmaßnahmen zur Risikominimierung kardialer Events getroffen werden.

Dieser Artikel fasst die aktuellen Sportempfehlungen für Erwachsene mit angeborenem Herzfehler unter Berücksichtigung der Befunde, der Medikation sowie der Wünsche und Erwartungen der Patienten zusammen. Da unerwünschte Ereignisse beim Sport stark mit den aktuellen Rest-Befunden zusammenhängen, ist es unerlässlich, die hämodynamische und elektrophysiologische Funktion in den Vordergrund zu stellen, und nicht den Vitiumtyp.

Bei der Mehrheit der Patienten können nahezu alle Sportarten empfohlen werden. Grundsätzlich sollten jährliche Kontrolluntersuchungen durchgeführt werden, um die Sportempfehlungen an die aktuellen Befunde anzupassen. Spezifische Restriktionen sollten ausschließlich im Falle von medizinischen Risiken ausgesprochen werden. Diese Restriktionen sollten mit jedem Patienten individuell, unter Berücksichtigung der aktuellen Befunde, Wünsche und Erwartungen des jeweiligen Patienten, besprochen werden.

Schlüsselwörter: Angeborene Herzfehler, Empfehlung, Einschränkung, Restbefund

Introduction

Physical activity is defined as any body movement executed by muscle contraction, leading to an additional energy consumption exceeding the basal metabolic rate. The American Heart Association emphasizes the importance of physically active lifestyles for the wellbeing and health of adults with congenital heart diseases.[24, 196-203] Several studies have shown an increase of the physical activity and health benefits due to physical exercise training as a part of the congenital heart disease management.[33] Furthermore, the improvement of exercise performance and promotion of physical activity is the aim of strategies dedicated to preventing the development or progression of heart diseases and to decreasing further risks in cardiovascular events. Even in patients with congenital heart diseases, structured exercise-based rehabilitation programs are an effective possibility in ensuring the greatest safety and optimal efficacy in decreasing the mortality and morbidity rate in patients with known cardiovascular diseases.[31]

Physical capacity is one of the most robust predictors of survival and health outcome of healthy people in general and cardiac patients, including those with congenital heart diseases.[19, 31] Poor physical capacity is associated with a higher risk for hospitalization or death.[30, 32, 204, 205] These facts are alarming since studies have shown reduced physical capacity in patients with congenital heart diseases, regardless of symptoms.[19, 30] Several studies demonstrate the improvement in the objective and subjective physical capacity due to physical activity and sports participation. Apart from this, there was no cumulative occurrence concerning cardiac events like arrhythmias or sudden deaths.[18] There is compelling evidence that physical activity improves cardiovascular and health benefits as well as the patient's quality of life.[24, 196, 206-210] Those data also apply to patients with congenital heart diseases. Nevertheless, precautions have to be taken in some cases and recommendations have to be made in order to minimize the risk of cardiac events.

Sport Eligibility Testing

The purpose of sport eligibility testing is a detailed cardiac-specific examination with the aim of identifying residuals with a specific risk for disastrous events during physical activity. Sport eligibility is solely dependent on the patient's risk that acute cardiac problems may occur related to activity or develop in long-term with certain exercise. Therefore, sport eligibility is not solely dependent on the physical capacity and only little on the initial congenital heart disease, but notably on the results of recent examinations.[211] Accordingly

necessary conditions are the precise knowledge of the heart disease, therapeutic steps and current cardiac situation including all residual findings.[211]

Sport eligibility testing consists of medical history (including a sport history), physical examination, electrocardiography (resting ECG, and Holter ECG), echocardiography and cardiopulmonary exercise testing.[212] (Table 4) In certain patients, an additional cardiac MRI or a CT scan might be necessary. All these investigations are designed to identify the age-appropriate development of cardiopulmonary status, heart rhythm, physical capacity as well as cardiac functionality and the hemodynamic significance of the residual findings, at rest and in exercise.[196-203, 212] The resting ECG gathers dysrhythmias, ischemia and signs of congenital heart diseases which are related to arrhythmias, like altered QT interval, signs of hypertrophy, repolarization disorders and pre-excitations.[211] The evaluation of the individual anatomical situation, residual findings and the cardiac function can be made on the basis of echocardiography. During the cardiopulmonary exercise testing, cardiorespiratory fitness is examined on the basis of the maximal oxygen uptake ($\dot{V}O_2$peak) measurement. Cardiorespiratory fitness is one aspect of physical fitness (representing endurance). Also arrhythmia, desaturation, drop in systolic blood pressure, or a circulatory failure on exercise have to be carefully analyzed in order to give an appropriate sport recommendation to the patient. Exercise echocardiography and invasive cardiopulmonary exercise test with pulmonary artery catheter is currently confined to scientific questions.

Clinical Considerations Relevant to Physical Activity

Correction of congenital heart diseases is thought to be achievable in the majority of the patients. However, residual findings are not rare. Some complex heart malformations, called functionally univentricular hearts, can only be palliated with a type of Fontan procedure that needs special consideration for sport counselling. At the time of sport eligibility testing, most of the heart defects are “corrected” and show more or less severe residual findings.[213] The initial congenital heart disease, its sequence of therapeutic interventions as well as the extent of the residual findings and the evaluation of the functions determine not only the patient’s physical capacity but also the patient’s individual risk.[212] In the vast majority of former international recommendations, sport eligibility was categorized exclusively on the basis of the underlying congenital heart disease. Since assigning a certain physical capacity to individual types of congenital heart disease has not turned out to be sensible, it is more useful

to focus on the hemodynamic function and to consider the unique clinical status than focusing on the type of defect (Table 5).[24, 212]

There are no restrictions for patients with an atrial or ventricular septal defect, patent ductus arteriosus, patent foramen ovale as well as an aortic isthmus stenosis, if no residuals are present. Those patients are allowed to participate in both in leisure sports and in competitive sports. Nevertheless, for example ventricular dysfunction, aortic abnormalities, syncope, hypoxia, anticoagulation and device implantation are morbidities that may influence sport eligibility.[24] Additionally, there are no restrictions in minor defects that do not need to be corrected and do not implicate complications. Furthermore, the following facts should be considered:

Ventricular Dysfunction

Patients with significant ventricular dysfunction are allowed to perform a wide range of leisure sports at low to moderate dynamic level, while these patients should be discouraged from performing competitive sports. However, static sport activities inducing an increase in blood pressure should be omitted. Thus, disciplines such as line bowling, walking, baseball, golf, cricket or tai chi are recommended. Patients who are also suffering from arrhythmia should follow the recommendations for physical activity published by the Heart Rhythm Society.[24]

Aortic Abnormalities

Aortic dilations are most notably in bicuspid aortic valves, aortic coarctation as well as in conotruncal defects which can occur in various forms of congenital heart diseases. The risk of dissection is largely related to the size of the aorta and its progression. Wall stress on the aorta depends on the rise of blood pressure during exercise. In general, dynamic activities of low to moderate intensity can be recommended to patients with a dilation of more than 2s.[24, 211] Static activities should be avoided due to the rise in blood pressure. Furthermore, sport disciplines associated with the risk of chest compression, as well as competitions invariably have to be avoided to prevent aortic dissection, especially at the insertion of the aortic ligament. In addition, the restrictions for patients with connective tissue diseases with aortic involvement like Marfan syndrome, Loeys Dietz syndrome or Ehlers Danlos syndrome might have to be extended depending on the individual medical findings.[211]

Syncope

If syncope occurs during exercise, physical activities should be avoided until the cause has been identified.[211] Even if there is no cardiac reason for syncope, patients at risk for syncope should not perform activities where they put themselves or companions in danger in the case of syncope. Those patients should participate in activities like soccer, walking, baseball, dancing, table tennis bowling, yoga and tai chi. Sports like gymnastics, horseback riding, diving and rock climbing should only be performed under supervision, if syncope episodes are common. If the patient suffers from cardiac syncope, sport eligibility is determined by the underlying congenital heart disease.[214]

Cyanosis

In some patients with congenital heart diseases, intracardiac shunting is diagnosed. In those patients physical activity can cause or increase cyanosis. Since increasing cyanosis usually limits exercise to an appropriate extent, medical activity restrictions do not need to be defined. Concerned patients should be encouraged to do sports within comfortable limits, even if the hypoxia increases related to exertion. In cyanotic patients, discomfort during exercise might be a first sign of cerebral hypoxia, therefore the current activity should be interrupted.[211] The precondition for being active is to ensure the opportunity for the patients to determine the activity intensity on their own.[24]

Pulmonary Hypertension

The same recommendations as for cyanosis can be made for patients with pulmonary hypertension and a right-left-shunt. Syncope and circulatory collapse might occur during exercise in patients with solely pulmonary hypertension and no shunt. Those patients are restricted to low dynamic and low static activities which should not be under performance pressure. If syncope is recorded in the medical history, physical exercises without medical monitoring have to be confined to the minimum.[211] Patients suffering from severe pulmonary hypertension should be allowed to perform leisure sports activities, however a specialized rehabilitation program is recommended at the beginning.[215, 216]

Arrhythmia

In case of supraventricular ectopy, no restrictions are necessary, unless there is high-grade arrhythmia. By contrast, ventricular ectopy could be a first sign for myocarditis, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy or other structural cardiac diseases associated with a higher risk of sudden death. In these instances, long-term electrocardiography, echocardiography and cardiopulmonary exercise testing should be implemented. Patients can perform any activities without any restrictions if they are free of symptoms and have an unremarkable echocardiography, normal PQ-time and monomorphic ectopy in the Holter ECG which disappears during exercise. Indeed, annual follow-ups should be performed to adjust the recommendations to the current cardiac situation.[211]

Patients with rare supraventricular tachycardia lasting for a few seconds and without any haemodynamic impairments are allowed to do sports. The same applies to patients with a structurally anomalous heart after a successful catheter ablation. No restrictions have to be set in this group.[211] A detailed rhythmological diagnostic investigation is warranted in case of ventricular tachycardia. Any exhausting physical activity has to be avoided until completion of the diagnosis.[211]

Ion Channel Diseases

Ion channel diseases are associated with a higher risk of sudden death. The most frequent ion channel diseases are short QT syndrome, Brugada syndrome, long QT syndrome and catecholaminergic polymorphic ventricular tachycardia. There is evidence that particularly the last two diseases cause life-threatening arrhythmia under stress and during physical exercises. Under certain circumstances, leisure sports can be performed if sudden load peaks, long workloads and performing sports in extreme heat or humidity are avoided.[211]

Cardiomyopathy

Cardiomyopathy is the most common cause of death in competitive sports. In individual cases, training schedules providing low workloads and designed according to the individual findings can be shaped. Currently there is no consistent recommendation for patients with non-compaction cardiomyopathy. Recommendations for those patients seem to depend on the dilative components. Patients with arrhythmogenic right ventricular cardiomyopathy showing

clinical symptoms are not allowed to perform any sports due to the risk of ventricular tachycardia.[211]

After Procedures

Supervised sport activities can be initiated a few days after procedures. Strenuous exercise should be delayed for approximately 1-2 weeks after catheter or 3-6 weeks after surgery, unless complications or residues occurred. Patients with a Fontan circulation are limited in their physical capacity, and confine themselves accordingly. These patients are allowed to take part in most of the leisure sport activities. In case of myocardial dysfunction, strength training should not be performed.[196] A Valsalva maneuver has to be avoided because of blocking the circulation in the lungs, as a consequence diving is not permissible.[211] Nevertheless these patients should be physically active. The opportunity to interrupt the exercise at any time should be given.[211] Furthermore, restrictions of ventricular dysfunction apply for Fontan patients.

Medical Drug Treatment

Taking anticoagulants poses a higher risk of bleeding during performing exercises which are associated with a higher risk for impact. The risk of undergoing impacts, especially those leading to intracranial hemorrhage, is increased for patients from the age of 14 playing more competitively.[196] Patients with anticoagulation should be admonished to participate in sports in which “impacts may occur” and discouraged to participate in sports where “impacts are expected”.[196] In sport disciplines implying an increased risk of blunt head traumas (such as martial arts), antiplatelet treatment should also be considered.[211] For more detailed information about performing exercise with oral anticoagulation, the readers are referred to the article “Sport unter oraler Antikoagulation bei Vorhofflimmern” being published in this issue.[217]

Device Implantation and other Implants

For pacemaker patients, engaging in physical exercises and activities is possible to a limited scope[202] It is essential to participate only in sports consistent with the limitations of the underlying heart disease as well as the current cardiac situation.[20, 211] Sport disciplines like

martial arts, football, rugby, hockey and boxing should be avoided under all circumstances due to unavoidable bodily collision. In these sports, there is a high risk of trauma such as direct blows to the chest damaging the pacemaker system or the risk of skin perforation which may occur after trauma.[20, 202] In order to avoid fractures in pacemaker leads, exercises with direct compression of the chest or excessive movement of the upper limbs as well as disciplines where overhead strokes are performed (e.g. volleyball) should also be prohibited.[202] Depending on the type of sports and the patient's arm dominance, the pacemaker should be implanted on the right or left side.[20] For example, the pacemaker should be implanted on the left side in a right-handed badminton player.[20]

In sport disciplines such as baseball, basketball and soccer, collisions are possible but less likely. Taking protective measures such as wearing a protective vest is recommended. When diving, the pacemaker system will be exposed to water pressure which can lead to penetration of fluid implicating a functional loss. The maximal diving depth is dependent on the implanted model and the manufacturer's data have to be taken into account.[211] Moreover, sports associated with a higher risk for the patient or the companion in the case of sudden presyncope or syncope should not be performed by pacemaker patients who recently had syncope. Those types of sports include rock climbing, skiing, motorsports, watersports and bicycle racing.[211]

The same recommendations apply for patients wearing an ICD. The essential prerequisite for risk-free sport is a precise ICD programming which depends on the kind of tachycardia and the individual peak heart rate achieved in exercise. Inappropriate shocks triggered by exercise-induced sinus tachycardia or arrhythmia have to be avoided.[218] In general, there are no reasons not to resume sporting activities six weeks after pacemaker or primary ICD implantation. After secondary ICD implantation or intervention with a shock or antitachycardiac pacing, sport activities should be deferred for 3-6 months.[218]

In general, there are no restrictions for patients with mechanical valves, stents, conduits, vascular closure devices or closure devices for atrial or ventricular septal defects unless there is verification of ventricular dysfunction, arrhythmia and other clinical considerations which are relevant to physical activity. There is no evidence for direct mechanical impairment of these implants due to any physical exercise.[211]

How to plan Exercise Training

One cornerstone of physical activity is exercise training which is planned, structured, repeated and targeted to improve physical fitness.[133] In patients with congenital heart disease, the type and severity of the heart disease have to be considered. Moreover, the patient's exercise training should be adjusted and structured individually on the basis of a risk evaluation. In addition, personal characteristics like sex, age, previous physical inactivity and exercise experiences, preferences, skills, motivation and training goals need to be taken into account.[212] Based on this information an individual recommendation, containing the training Frequency, exercise Intensity, workout Time as well as the Type of exercise (FITT principle) should be determined for every patient. Furthermore training method, type of training and the training goal should also be defined. Individual training schedules should be designed in a team of physiotherapists and cardiologists specializing in congenital heart diseases.[208]

The training frequency and the workout time should include the duration of the whole training schedule and of every single training session. The exercise intensity can be determined for endurance training by the heart rate and derived from a certain level of oxygen uptake or lactate accumulation. The heart rate can be supervised by the patient during exercise. It is recommended to consider the patient's individual physical capacity as well as the specific conditions, to start at low level and to increase the exercise intensity, training frequency and workout time slowly but steadily.[212]

In general, High Intensity Training (HIT) and High Intensity Interval Training (HIIT) represent forms of training with the aim of performing at the highest possible intensity at maximum heart rate. Stress phases are followed by given recovery phases in which activities are performed at low intensities. These training sessions are exclusively recommended for a short time and especially under supervision as acute side effects may occur.[219]

Furthermore, exercise can be performed in a dynamic and static way. The main difference between dynamic and static exercise is that high pressure load is verified by static exercise whereas a volume load can be evidenced during dynamic exercises.[196] Predominantly dynamic exercises are associated with a protective effect on the cardiovascular system caused by the reduction in left ventricular afterload in long-term.[212] They are the preferred mode of training from a cardiologists' point of view when dealing mainly with left heart failure caused by coronary artery disease.[206] Predominantly static exercise (maximal strength training) induces muscle growth and is the favorite training modality to increase strength and body shaping. During static exercise, however, high pressure loads on the systemic circulation can

extremely influence the hemodynamic situation in patients with previous left heart damage. Metabolic and mechanical afferents in skeletal muscle induce large persistent changes in blood pressure.[196, 212] In contrast to maximal strength training, where hypertrophy has priority, dynamic strength training is characterized as strength endurance training. Training with submaximal intensity and a higher number of repetitions leads to a mid-term reduction in arterial blood pressure.[219] The intensity of static and dynamic exercises is commonly divided into three different levels: low, medium and high. The classification refers to the exercise intensity which is performed during competition, since in training different intensities might occur.

A detailed classification of sports according their degree of impact is given in (Table 6) for adolescent athletes. When the occurrence of sudden syncopal events poses risks to the athletes or others in certain sport types, these risks are classified as well. This classification is based on the distribution by Maron, who associated the types of sports with the educational background (Junior High School vs. High School / College). The older the athletes, the higher the risk that impact may occur. With advancing age, muscular strength increases and movements are more powerful. Furthermore, the will to win is more pronounced. Thus, there is a higher probability of getting injured. Maybe the same classification could also be applied to leisure versus competitive sport activities. This classification is a useful tool for making recommendations concerning sport eligibility and guiding practitioners. Nevertheless, it should be noted that this scheme is just a rough and simple guidance for orientation. For instance, different positions on the court causing different cardiovascular loads have not been taken into account. It is indispensable that the individual patient as well as the way of performance and the playing position be considered to enable a reliable recommendation.[196]

There are no data that the general training principles are different in patients with congenital heart disease. All training activities train the components that are used in the training. Aerobic training improves aerobic capacity, strength training improves strength, and flexibility training improves flexibility. The usual thresholds from sport physiology can be used to set up a training plan; however the individual thresholds have to be tested and must not be substituted by various normative data or rules of the thumb.

Practical advices for cardiologists

Findings from several studies indicate that neither advices in routine consultations nor intensive interventions render persistent increase in patient's physical activity.[208, 209] In order to increase patient's daily activity and their exercise activity sustainably, the following issues should be heeded:

In general, all rehabilitation and leisure sport activities can be recommended for most patients. These patients should be allowed to do sports as physically possible and reasonable. Fundamentally, annual follow-ups need to be conducted to reassess the sport recommendations considering recent diagnostic findings.[202, 218] Specific restrictions should only be addressed in case of medical issues.[212] These restrictions should be discussed individually with the patient, taking any diagnostic findings and the patient's requests as well as their expectations into account. In any case of uncertainty on the part of patients or cardiologists, further experts (e.g. exercise physiologists) should be called in for additional examinations or additional advice. Specific sports groups for patients with congenital heart diseases may give a first insight on the patients' capability in sports and alleviate any baseless fears. Nevertheless, in long-term, most patients can join regular sport clubs with no risks.

In general, recommendations for increasing physical activity need to be adjusted to every patient's daily routine, as individualized interventions are more successful.[208] Physical activities should be manifold to motivate the patients, provide pleasure, and promote social cohesion. Having fun is one of the main reasons for many patients to remain physically active. Risk-free physical activity can be integrated in the patient's daily life solely by tailored recommendations considering recent diagnostic findings, medication, and considering patient's requests and expectations.

Tables

Table 4: Cardiological assessment to define sport eligibility in patients with congenital heart disease

EXAMINATION	PURPOSE
Medical history	Current symptoms, health history, dispositions, living conditions, etc.
Physical examination	Age-appropriate development of cardiopulmonary status, palpitation, auscultation and blood pressure behavior
Electrocardiography	Arrhythmia, time intervals, depolarisation, repolarisation, abnormalities
Echocardiography	Cardiac functionality and hemodynamic and significance of residual findings
Cardiopulmonary exercise testing	Cardiac Rhythm and blood pressure behavior during exercise and peak cardiopulmonary exercise capacity
Cardiac magnetic resonance, computed tomography (in certain patients)	Anatomical and functional details

Modified from[19] with permission (copyright 2007 Deutsches Äerzteblatt)

Table 5: Restrictions depending on residual findings

CLINICAL CONSIDERATIONS	RESTRICTIONS
Ventricular Dysfunction	
	No participation in competition. Sport permission can be expressed for leisure sports activities, however it should be restricted to low to moderate dynamic and static activities.
Arrhythmia	
Supraventricular ectopy and tachycardia	No participation in competition until success of treatment is proven in symptomatic supraventricular tachycardia. None, if the tachycardia is rare, short in duration and self-limiting without any hemodynamic impairment.
Ventricular ectopy and tachycardia	None, if patients with ectopy are asymptomatic, the extrasystoles are monomorphic and the number is decreasing with exercise. Patients with ideoventricular rhythm or idiopathic monomorphic ventricular tachycardia can exercise if they are not symptomatic, short and non-sustained. No exercise until diagnostic workup is complete.
Ion Channel Diseases	
	Leisure sports activities might be performed according the genetic variants, EKG findings, and success of treatment.
Cardiomyopathy	
	Sport permission can be expressed for leisure sports activities depending on the findings and, in individual cases, additionally low-intense physical exercises might be allowed.
Syncope	
Syncope	No exercise until clarification of the syncope reasons. No activities where they put oneself or companions in danger in the case of syncope.
Reflex Syncope	No exercise until clarification of the syncope reasons. No restrictions in reflex syncopes.
Cyanosis	
	None, as long as the patient is subjectively completely asymptomatic and is allowed to determine his/her own activity intensity.
Pulmonary Hypertension	
	None for patients with pulmonary hypertension and a right-left-shunt, as long as the patient is free of symptoms and is allowed to determine his/her own activity intensity. Patients having no shunt are restricted to leisure sports with low dynamic and low static activities.
Medical Devices	
Pacemaker	Sport permission can be expressed for low-intensity and moderate-intensity sport disciplines unless device and leads are endangered by expected collisions and impacts, high pressure load (diving depending on manufacturer specifications), or frequent and intensive upper limb movements. Exercise prohibition of sport disciplines where sudden presyncopes or syncopes correlate with an increased risk for the patient or accompanying persons.
ICD	Sport permission is according to the underlying disease. Exercise prohibition of sport disciplines where collisions and impacts are expected, diving (depending on manufacturer specifications) and sport disciplines with frequent and intensive movement of the upper limbs. Exercise prohibition of sport disciplines where sudden presyncopes or syncopes correlate with an increased risk for the patient three months after ICD-implantation or shock.
Other Devices	No exercise prohibition for patients with artificial heart valves, stents, conduits or other devices unless direct impact on the device is expected.
Aortic Abnormalities	
Aortic Dilatation	Exercise prohibition of high-intensity dynamic and any static exercise, as well as disciplines with a risk of thorax compression. Exercise prohibition has to be extended in patients with connective tissue diseases with aortic involvement depending on the individual findings.
Aortic Dissection	Sport permission can only be expressed for low-intensity dynamic and static leisure sports activities for patients with a dissection of the descended aorta which does not need any surgery, depending on the pathology, findings and the inclination of the progression.
Anticoagulation	
	Exercise prohibition of all contact sport disciplines.
After Procedures	
After Surgery	Supervised rehabilitation can start immediately according to the clinical condition. Full sport permission can be expressed six weeks after a sternotomy even for static sports activities and contact sports unless other restrictions are present.
After Cardiac Catheter	Full sport permission can be expressed at least one or two weeks afterwards, unless complications or residues occurred.

Table 6: Sports according to risk of impact and age

	COMPETITIVE SPORTS	LEISURE SPORTS
Impact expected	American football	American football
	Ice hockey	Ice hockey
	Lacrosse	Lacrosse
	Wrestling	Wrestling
	Karate / Judo	Karate / Judo
	Fencing	Fencing
	Boxing	Boxing
	Downhill skiing	
	Squash	
	Basketball	
	Soccer	
Impact may occur	Field hockey	Field hockey
	Equestrian	Equestrian
	Cycling	Cycling
	Gymnastics	Downhill skiing
	Baseball / Softball	Squash
	Figure skating	Basketball
		Soccer
Impact not expected	Cricket	Cricket
	Golf	Golf
	Riflery	Riflery
	Volleyball	Volleyball
	Swimming	Swimming
	Track and field	Track and field
	Tennis	Tennis
	Cross-country skiing	Cross-country skiing
	Rowing	Rowing
	Sailing	Sailing
	Archery	Archery
	Weightlifting	Weightlifting
	Badminton	Badminton
		Gymnastics
		Baseball / Softball
		Figure skating

Modified from[206] with permission

5.2 Reduced Parasympathetic Activity in Patients with Different Types of Congenital Heart Disease and Associations to Exercise Capacity

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First Author:	Celina Fritz
Current Status:	Under Review; Journal of Cardiopulmonary Rehabilitation and Prevention

Individual contribution:

The research idea investigating the HRV in patients with CHD using VNS analysis professional software was developed by me. I was responsible for the procurement of the required materials and co-responsible for the conception and the design of the study. I performed the measurements in the department of congenital heart disease and pediatric cardiology of the German Heart Centre Munich. Quantifying the activity of the ANS in this special patient group became a new field of research in this outpatient clinic. After I had collected the data of the HRV measurement and the CPET, I analyzed them. I wrote the manuscript, accordingly, I represent the main author of this paper and was mainly responsible for the submission.

All actions were taken in consultation with the co-authors, who supported me from the development of the research idea to the completion of the paper. PD Dr. Jan Müller and Prof. Dr. Alfred Hager were responsible for conception and design of the study and responsible for data monitoring and integrity. Prof. Dr. Renate Oberhoffer and Prof. Dr. Peter Ewert contributed to the design and conception of the study. Julia Hock provided support with the data collection. All authors gave important input for revising and improving the quality of the manuscript.

Summary and main results:

The primary aim of this study was the evaluation of the parasympathetic activity in patients with various CHD to quantify the ANS activity by capturing the HRV. The second aim was to examine a possible association of parasympathetic activity and exercise capacity in patients with CHD, gathered from the CPET, potentially offering a therapeutic approach to reduce mortality and morbidity in these patients.

Two hundred and twenty-two patients (44.5% female, 28.4 ± 10.1 years old) with different types of CHD underwent a HRV measurement and a CPET in the outpatient visit of the German Heart Centre in Munich. The various CHD were classified into the four major subgroups, namely: “Left Heart Obstruction” (LHO), “Right Heart Obstruction” (RHO), “Transposition of the Great Arteries” (TGA) and “Fontan Circulation” and a miscellaneous group. Additionally, the heart defect severity was defined as simple, moderate or complex. The healthy control group (CG) consisted of 57 healthy volunteers (61.4% female; 29.0 ± 7.1 years).

During breath-controlled HRV measurement in supine position, the RR-intervals of 130 adjacent heartbeats were recorded. By means of the parameter RMSSD the parasympathetic activity was evaluated. For statistical analysis RMSSD was used after logarithmic transformation to achieve normal distribution. Additionally all patients underwent an incremental symptom-limited CPET until exhaustion on a bicycle ergometer according to recent guidelines. Peak oxygen uptake ($\dot{V}O_2$peak), representing exercise capacity, was calculated as the highest mean oxygen consumption obtained during any 30-second time interval.

Patients with CHD showed a significant reduced parasympathetic activity by means of a lnRMSSD in comparison to the CG after adjustment for covariates age, sex and heart rate (CHD: 3.55 ± 0.57 vs. CG: 3.93 ± 0.55; p<.001). In comparison to healthy CG patients with RHO (3.60 ± 0.54; p=.014), TGA (3.49 ± 0.55; p=.046), Fontan Circulation (3.07 ± 0.54; p<.001) and in the miscellaneous group (3.61 ± 0.55; p=.001) demonstrated significant reduced parasympathetic activity, but not patients with LHO (3.74 ± 0.55; p=.948). Considering the heart defect severity, patients with complex CHD (3.40 ± 0.54 ms; p<.001) showed the lowest lnRMSSD values in comparison to the healthy CG (3.93 ± 0.55 ms) as well as simple (3.87 ± 0.55 ms; p<.001) and moderate CHD defects (3.74 ± 0.54 ms; p<.001).

Exercise capacity in patients with CHD was significantly reduced compared to the CG (CHD: 27.7 ± 8.3 ml/kg/min vs. CG: 37.5 ± 8.1 ml/kg/min; p<.001) which corresponded with peak oxygen uptake in percentage of predicted reference value in patients with CHD (78.9 ± 18.5 %). However, higher parasympathetic activity was moderately associated with an increase in peak oxygen uptake (r=.322; p<.001).

The major finding of this study was that patients with different types of CHD and especially patients with complex lesions showed significantly reduced parasympathetic activity in

comparison to a healthy CG and particular diagnostic subgroups of CHD. All diagnostic subgroups, except patients with left heart obstruction, showed a decreased parasympathetic activity.

Patients with CHD showed lower parasympathetic activity compared to the CG. Furthermore, an impaired parasympathetic activity was associated with a reduced exercise capacity. Therapeutic interventions implicating physical activity could result in an increased exercise capacity and an improved balance of the ANS.

Reduced Parasympathetic Activity in Patients with Different Types of Congenital Heart Disease and Associations to Exercise Capacity

Abstract

Purpose: Current research indicates an imbalance in the autonomic nervous system (ANS) pathways activities in patients with congenital heart disease (CHD). The heart rate variability (HRV) is a measure to quantify the parasympathetic and sympathetic branches' activities. This study evaluates the parasympathetic activity by means of HRV in patients with CHD regarding diagnostic subgroups and CHD severity and their association to exercise capacity.

Methods: From July 2016 to August 2018, a total of 222 patients with different types of CHD (44.5% female; 28.4 ± 10.1 years) received breathing controlled HRV measurement in supine position. Based on 130 adjacent heartbeats, the root mean square of successive differences (RMSSD), a parasympathetic activity surrogate, was estimated and log-transformed. Additionally, all patients underwent a cardiopulmonary exercise test. For comparison, a control group (CG) of 57 (61.4% female; 29.0 ± 7.1 years) healthy volunteers was recruited.

Results: Patients with CHD exhibited reduced parasympathetic activity in comparison to the CG (lnRMSSD CHD: 3.55 ± 0.57ms vs. CG: 3.93 ± 0.55ms; p<.001), with the lowest parasympathetic activity in patients with Fontan Circulation (3.07 ± 0.54 p<.001). Complex CHD (3.40 ± 0.54ms) had worse values compared to patients with simple (3.87 ± 0.55ms; p<.001) and moderate severity (3.74 ± 0.54ms; p<.001). Better parasympathetic activity in CHD patients was associated with increased exercise capacity (r=.322; p<.001).

Conclusions: Impaired parasympathetic activity suggests limited function of the ANS in CHD patients. Further studies should focus on the association of exercise capacity and ANS to possibly improve parasympathetic activity and functional outcomes.

Keywords: Parasympathetic Nervous System, Vagal Activity, Peak Exercise Capacity

Condensed Abstract

Heart rate variability measurement and a cardiopulmonary exercise test were performed in 222 patients with congenital heart disease (CHD) and 57 healthy controls. Patients with CHD showed reduced parasympathetic activity and exercise capacity compared to the controls.

Impaired physical activity suggests limited function of the autonomic nervous system in CHD patients.

Introduction

Heart rate variability (HRV) assessment is used as a non-invasive method to quantify the activity of the autonomic nervous system (ANS). ANS is comprised of the sympathetic and parasympathetic or vagal pathways regulating heart rate and rhythm as well as sustaining its electrical stability.[220, 221] An impaired HRV is associated with reduced parasympathetic and increased sympathetic activities, which goes along with cardiac electrical instability and is an independent predictor of arrhythmic complications and mortality.[36, 37] Not only patients with impaired HRV who are additionally suffering from pathological conditions, such as heart failure, myocardial infarction, and arrhythmia, but also patients with congenital heart disease (CHD) have an increased risk of cardiac death.[37, 222, 223]

Disagreement concerning the parasympathetic activity level in the previous studies dealing with patients with CHD may be due to the different measuring methods, small and inhomogeneous subgroups, and very often the lack of a control group (CG). An indication of a broad limitation of the ANS, reflecting impaired parasympathetic activity, seems to exist in a vast majority of patients with CHD.[38-40, 224] Since open-heart surgery may result in myocardial damage, this autonomic imbalance in CHD patients seems to be attributable to the initial damage of the ANS during surgery.[225] Moreover, the elevated right ventricular end systolic volumes, pulmonary regurgitation, reduced ventricular ejection fraction, and widening of the QRS complex have also shown to be associated with ANS impairments.[224, 226, 227]

Apart from analyzing the cardiovascular autonomic control, the exercise capacity assessment is an essential predictor of mortality and morbidity in patients with CHD.[25-27, 30] The improvement of exercise capacity has a positive effect on the health status in patients with atrial septal defects type II.[228] A systematic review and meta-analysis of exercise training in adult patients with CHD indicates that exercise training is associated with a significant improvement in exercise capacity.[229] Since increased parasympathetic and reduced

sympathetic activities go along with better exercise capacity, it has been shown that there is a link between the ANS and exercise capacity in the general population.[28, 34] Whether this association is present in patients with CHD is currently not clear, however, a possible association would offer a potential therapeutic approach in reducing mortality and morbidity.

The primary aim of this study was to analyze the parasympathetic activity of the ANS by means of the HRV in patients with CHD, according to diagnostic subgroups and severity, and to compare these patients with a healthy CG. Secondly, a possible association of the parasympathetic activity and exercise capacity in patients with CHD was evaluated.

Patients and Methods

Study subjects

HRV and cardiopulmonary exercise test (CPX) data of 222 patients (28.4 ± 10.1 years; 16 to 49 years; 44.5% female) with various CHD were collected from the outpatient clinic at the German Heart Centre in Munich from July 2016 to August 2018. The CHD patients were classified into four subgroups, namely: "Left Heart Obstruction" (LHO), including aortic stenosis, aortic insufficiency, and coarctation of the aorta; "Right Heart Obstruction" (RHO), including tetralogy of Fallot, pulmonary stenosis, and pulmonary insufficiency; "Transposition of the Great Arteries" (TGA), including all different types of surgeries; and "Fontan Circulation" including patients after Fontan palliation (Fontan; Figure 27). Heart defect severity was defined as simple, moderate or complex according to the American College of Cardiology classification.[12] Last surgery of the patients was at least twelve months ago, and the last cardiac catheter examination was six months prior to inclusion. This time period was not decisive for the date of the HRV measurement. None of the patients had a pacemaker. Patients' HRV data was compared to a CG which consisted of 57 healthy volunteers (61.4% female; 29.0 ± 7.1 years).

This study was conducted in accordance with the Declaration of Helsinki (revision 2008) and the Good Clinical Practice guidelines. Furthermore, the study protocol was approved by the local ethical board (project number 64/17S) of the Technical University of Munich. All participants gave written informed consent and agreed to an anonymous publication of their data.

Measurement of the autonomic nervous system (ANS)

The function of the ANS was quantified non-invasive and breath-controlled via the HRV measurement with the VNS Analysis Professional Software (Commit GmbH, Liebenburg, Germany). Subsequent to a 3-minute resting phase, 130 adjacent heartbeats were recorded. The patients were in the supine position and were instructed to relax and pace breaths in time to a visual signal (6 breaths/min) during the measurement. RR-intervals were recorded with the aid of an established high-resolution HRV chest strap system with bipolar chest leads. Therefore, it is in accordance with the guidelines for detecting slight RR-fluctuations.[156] With guarantee of quality measurement the accuracy of the parameters' computation is adjusted regularly with the scientific reference software Kubios HRV 2.1.[230] This validation of the software ensures a reliable measurement device for the HRV and complies with high scientific standards.

For statistical analysis the root mean square of successive differences (RMSSD), a parameter of the parasympathetic activity was used after the logarithmic transformation to achieve normal distribution.

Measurement of exercise capacity

All CHD patients underwent an incremental symptom-limited CPX until exhaustion on an electronically braked bicycle ergometer in upright position according to recent guidelines.[26] Subsequent to a 3-minute resting period to define the baseline, a 3-minute warm-up period without load was started. To determine each subject's limit of tolerance within 8 to 12 minutes after warm-up, a ramp wise load increase with 10, 15, 20, 30 or 40 W/min was used, based on the probable expected exercise capacity estimated by the investigator. After total exhaustion, a 5-minute recovery period proceeded while patients maintained cycling for 2 minutes with minimal load and a 3-minute period of sitting rest position. The patients were pedaling at a constant cadence between 60-80 revolutions per minute. Ventilation and gas exchange were measured via a breath-by-breath gas exchange analysis (Vmax 229, SensorMedics, Viasys Healthcare, Yorba Linda, California, USA). Simultaneously, a 12-lead electrocardiogram (ECG) was recorded along with peripheral oxygen saturation at rest, throughout the exercise protocol and during recovery. Furthermore, blood pressure measurements were taken every two minutes during the entire examination. Peak oxygen uptake (VO_2peak) was calculated as the highest mean oxygen consumption obtained during any 30-second time interval.

The reference values for age, body mass, body height, and gender, expressed in ‘‘% predicted’’ were calculated as previously described, and the peak heart rate reference values were calculated according to Tanaka and colleagues as follows: 208 - 0.7 x age.[231, 232] The compliance criteria for a valid CPX were achieved when either respiratory exchange ratio (RER) was ≥1.05, or peak heart rate was ≥85%. The cyanotic patients (oxygen saturation <90% at rest or at peak exercise) were included in the study independent of those criteria, since those patients were rarely able to reach the above mentioned thresholds.[233, 234]

Data analysis

Descriptive data of patients with CHD and the CG are shown in mean values and standard deviations (mean ± SD). The RMSSD values are expressed as the natural logarithm (lnRMSSD) of original units to achieve normal distribution that was confirmed by the Kolmogorov Smirnov test. The patient’s anthropometric data were compared with the CG using the Student’s t-test for unpaired samples. The mean differences (MD) in lnRMSSD between the groups were estimated using a general linear model with covariates sex, age, and heart rate and the Bonferroni *post hoc* test. Only within patients with CHD, the correlation between lnRMSSD and VO_2peak was evaluated using Pearson correlation analysis, after adjusting for CHD severity.

All analyses were performed using the SPSS (version 23.0, IBM Corporation, Armonk, NY, USA) and a two-tailed probability value <.05 was considered as statistically significant for all tests.

Results

Patients with CHD had a significantly reduced parasympathetic activity by means of the lnRMSSD in comparison to the CG after adjustment for covariates age, sex, and heart rate (CHD: 3.55 ± 0.57 vs. CG: 3.93 ± 0.55; p<.001). Study characteristics are displayed in Table 7, and a detailed overview of the diagnostic subgroup comparison is in Table 8 and Figure 28. After correction for age, sex, and heart rate, significant differences in parasympathetic activity in comparison to the healthy CG by means of the lnRMSSD were found in patients with RHO (p=.014), TGA (p=.046), Fontan Circulation (p<.001), and in the miscellaneous group (p=.001) but not for patients with LHO (p=.948).

Patients with complex CHD severity (3.40 ± 0.54 ms; p<.001) showed the lowest lnRMSSD values in comparison to the healthy CG (3.93 ± 0.55 ms) as well as the simple (3.87 ± 0.55 ms; p<.001) and moderate CHD defects (3.74 ± 0.54 ms; p<.001) (Figure 29).

In patients with CHD exercise capacity was significantly reduced compared to the CG (CHD: 27.7 ± 8.3 ml/kg/min vs. CG: 37.5 ± 8.1 ml/kg/min; p<.001) which corresponded with the peak oxygen uptake in % of predicted reference value in patients with CHD (78.9 ± 18.5 %). However, higher parasympathetic activity, expressed as higher lnRMSSD values, was moderately associated with an increase in peak oxygen consumption (VO2peak), representing exercise capacity (r=.322; p<.001), even after adjusting for CHD severity.

Discussion

Patients with different types of CHD showed significantly reduced parasympathetic activity, compared to a healthy CG. Further, patients with complex lesions had significantly reduced lnRMSSD regarding CHD severity. According to the diagnostic subgroups, patients with Fontan circulation had the most impaired parasympathetic activity. Furthermore, an impaired parasympathetic activity was associated with a reduced exercise capacity in patients with CHD.

ANS and Congenital Heart Disease

Several studies previously performed HRV measurements in patients with CHD and found an imbalance of the ANS in almost all kinds of these patients. The major culprit for this imbalance in this cohort is the myocardial damage due to surgical intervention(s) in infancy, where cardiac surgical repair causes myocardial scars and fibrotic tissue that may result in electrically unexcitable regions. According to severity, significant differences could be observed within the present examination. Patients with complex CHD severity had the most impaired parasympathetic activity in comparison to the healthy CG as well as simple and moderate CHD defects. It needs to be taken into account that in general, the vast majority of patients who have to undergo surgery have moderate or complex lesions.[225] In addition, patients with CHD often present elevated right ventricular end systolic volumes, pulmonary regurgitation, reduced right and left ventricular ejection fraction, and a widening of the QRS complex. All have a negative effect on the ANS by either increasing the sympathetic or decreasing the parasympathetic activity.[38, 224]

Baroreflex mechanism has been recognized as a key part of cardiovascular regulation.[224, 235] Studies in CHD indicate that cardiac surgical interventions impair the sympathovagal balance,

possibly provoking arrhythmia like ventricular fibrillation, ventricular tachycardia, and sudden cardiac death and increasing the risk of mortality, particularly in patients with systolic dysfunction.[37, 221, 224, 227, 236]

ANS and Diagnostic Subgroups

Regarding the diagnostic subgroups, significant differences could be observed. Patients who underwent Fontan surgery had the most impaired parasympathetic activity within the presented examination. This result is in agreement with many other studies that showed ANS imbalance independently from hemodynamics, the type of surgery or its quantity as well as the length of the follow-up or the age at repair.[39-41, 220] In our cohort, significantly impaired HRV values could be detected in comparison with both the CG and every single diagnostic subgroup. Functional univentricular hearts implicate increased pulmonary vascular resistance, chronically increased central venous pressure, intraoperative damage of the sinus node as well as increased pressure in the systemic and reduced pressure in the pulmonary veins.[220, 237]

Considering the diagnostic subgroups with biventricular repair, almost all patient groups have impaired parasympathetic activity in comparison with the CG except for patients with left heart obstruction. In accordance with other studies in patients with TGA we found reduced lnRMSSD.[238, 239] In those older TGA patients who underwent atrial switch surgery concerns causing autonomic imbalance were interatrial shunts and baffle obstructions limiting the systemic and pulmonary blood flow as well as arrhythmia.[240]

In patients with tetralogy of Fallot or Fallot type hemodynamics, significant global impairment of the ANS was observed in majority of the studies.[38, 224, 241, 242] Prolonged QRS duration, pulmonary regurgitation, and right ventricular overloading were related to the impaired ANS function and further trigger arrhythmia and sudden cardiac death.[38, 224, 241, 242]
In our study, patients with LHO exclusively exhibit an optimal parasympathetic activity, probably due to a higher number of native conditions and fewer numbers of surgical interventions. Additionally, these patients suffer less from conditions like volume overload or impaired ventricular hemodynamics. In this diagnostic subgroup, parasympathetic re-innervation increased significantly within the first year after valve replacement, and in children with coarctation of the aorta five years after surgery, implicating normalization of the parasympathetic and sympathetic activity over time.[243, 244]

ANS and Exercise Capacity

Patients with CHD showed lower peak exercise capacity in terms of oxygen uptake compared to the CG. This fact is of concern, since exercise capacity is still the strongest predictor of mortality and morbidity in patients with CHD.[27] However, the novel character of this study is that the parasympathetic activity was moderately associated with the peak oxygen uptake, a finding that was so far only reported in patients with tetralogy of Fallot.[245] In healthy individuals, this association has already been observed and exercise training has been shown to increase the parasympathetic activity along with exercise capacity.[28, 34] In patients with tetralogy of Fallot, Novakovic and colleagues recently pointed out that exercise training might also increase the ANS function and exercise capacity in these patients.[246] Since these two systems seem to be coupled in patients with CHD, therapeutic interventions like moderate endurance training, for instance walking, running, and swimming or relaxation techniques such as yoga, Pilates or progressive muscle relaxation could be recommended. In addition, these interventions might likely increase exercise capacity and restore the balance of the ANS, resulting in a decreased morbidity and mortality.

Conclusion

In conclusion, patients with CHD showed impairments in the parasympathetic activity compared to a healthy CG. All the diagnostic subgroups, except for the patients with left heart obstruction, showed a decreased parasympathetic activity by means of lnRMSSD. Patients with complex CHD severity and especially patients with Fontan circulation had the most impaired parasympathetic activity in comparison to the healthy CG and regarding CHD severity as well as diagnostic subgroups. Meanwhile, the impaired parasympathetic activity is associated with reduced exercise capacity, various therapeutic measures may be appropriate to improve the prognosis of patients. Therefore, larger studies are warranted in order to gain more insight into HRV values of adolescent and adult patients with CHD.

Limitations

In this study, only the time domain indices were evaluated. For a more accurate measurement and more precise comparison with other studies, frequency domain indices should be additionally gathered. To confirm these recent findings and to improve their validity, long-term measurements (e.g. 24-hour ambulatory ECG) need to be considered. Since our

examined short-term measurement only reflects a 2-minute snapshot at rest, the gathered HRV values might not be equitable with the real resting HRV values.

The CG was not age and gender matched. There was no significant difference in age; however, there were more females in the CG. To precisely identify the normal values of HRV within the diagnostic subgroups, the normal values of the parasympathetic activity need to be established from the reference subjects matched for gender, age, hemodynamic status, and cardiac anatomy. Moreover, the exercise capacity was only assessed in half of the controls.

The subgroups consisting of larger number of study patients were essential for taking quantity and different types of surgery into account as well as to ensure statistical statements. The number of native patients, surgeries, re-operations, and catheter interventions depends on the CHD and differs with respect to the diagnostic subgroups. In addition, more severe and complex lesions might be overrepresented, due to the fact that our institution is a specialized tertiary center. Furthermore, the study lacked corrections for other covariates such as differences in food and drink intake, and daytime and smoking habits that were not assessed in this study but are associated with HRV measures. The time period between surgery or cardiac catheter intervention and HRV measurement was dependent on the appointment at the outpatient clinic. The available results do not allow conclusions to be drawn about the impact of CHD or surgery on HRV. Lastly, the current data do not allow conclusions to be made as to whether good exercise capacity or the type of surgery influences HRV.

Figures

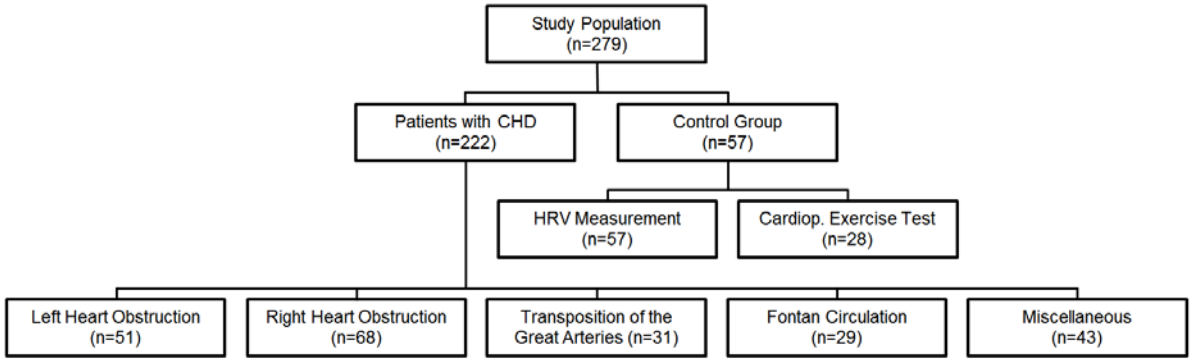

Figure 27: Study population, selection of patients with congenital heart disease and diagnostic subgroup classification

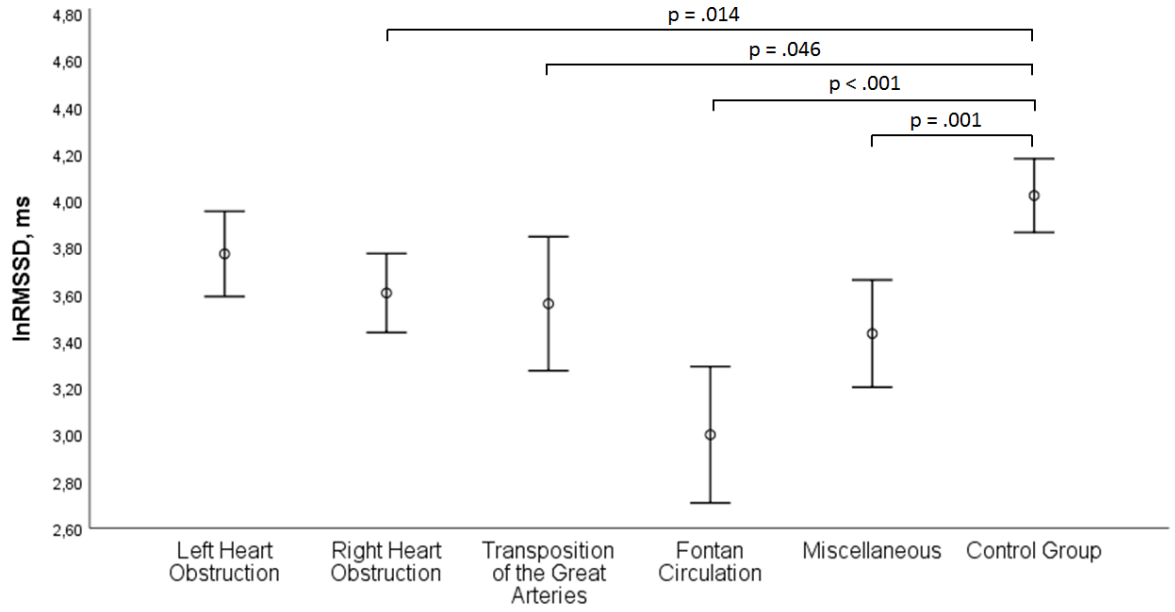

Figure 28: Mean difference and standard error of natural logarithm of root mean square of successive differences for patients with congenital heart disease compared to the control group, corrected for sex, age and heart rate

lnRMSSD: natural logarithm of root mean square of successive differences; ms: milliseconds

Mean and 95% Confidence interval of the standard error adjusted for sex, age and heart rate, significance value was set to ≤.05

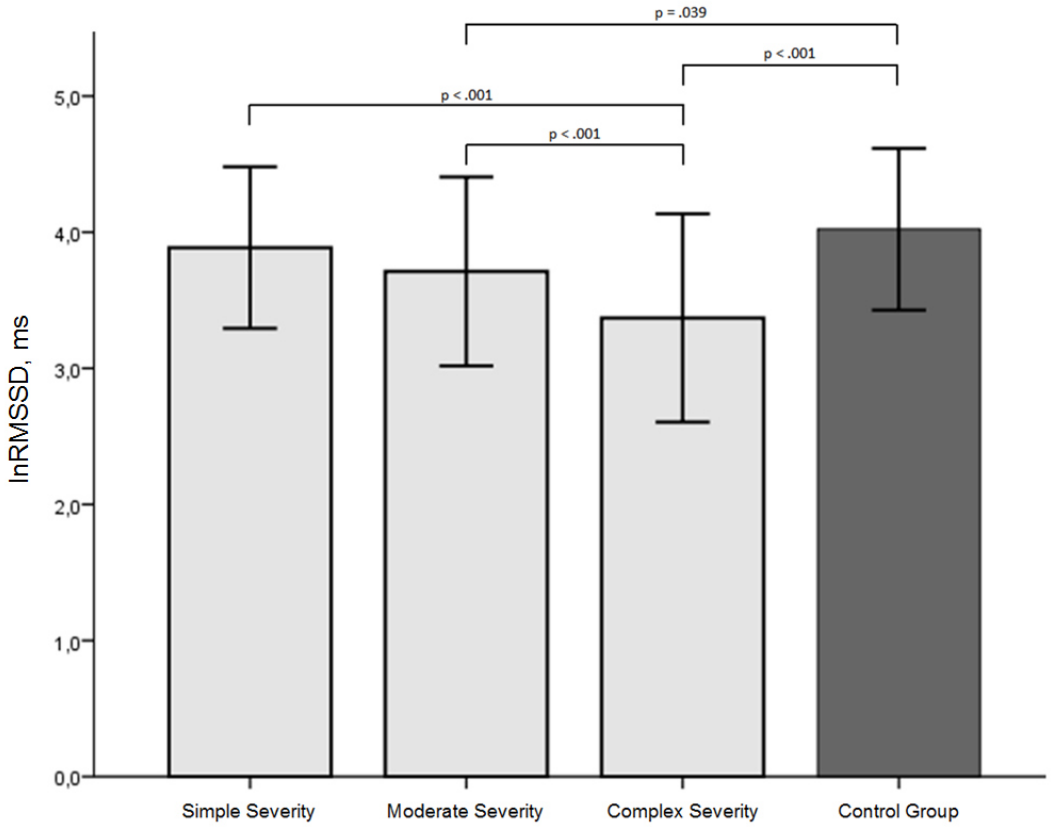

Figure 29: Mean difference of natural logarithm of root mean square of successive differences for patients with congenital heart disease, according to severity, compared to the control group, corrected for sex, age and heart rate
lnRMSSD: natural logarithm of root mean square of successive differences; ms: milliseconds
Mean ± standard deviation, significance value was set to ≤.05

Tables

Table 7: Comparison of patients with congenital heart disease and the control group

	Patients with CHD[n] (n=222)	Control Group (n=57)	p-value
Anthropometrics			
Gender, female	151 (44.5%)	35 (61.4%)	**.017**
Age, years	28.4 ± 10.1	29.0 ± 7.1	.596
Height, cm[a]	171.4 ± 9.2	173.7 ± 8.5	.105
Weight, kg[b]	69.6 ± 14.3	67.7 ± 11.5	.364
BMI[c], kg/m^{2}[d]	23.6 ± 4.1	22.3 ± 2.6	**.006**
Autonomic Nervous System			
Heart rate, bpm[e]	73 ± 12	69 ± 10	**.021**
RMSSD[f], ms[g]	44.0 ± 33.2	65.3 ± 35.0	**<.001**
lnRMSSD[h], ms	3.52 ± 0.75	4.02 ± 0.59	**<.001**
lnRMSSD, ms (adjusted)*	3.55 ± 0.57	3.93 ± 0.55	**<.001**
Exercise Capacity			
VO_2peak[i], ml/kg/min[j]	27.5 ± 8.3	37.5 ± 8.1	**<.001**
VO_2predicted, %	78.4 ± 18.7	116.8 ± 24.7	**<.001**
VE/VCO_2slope[k]	28.3 ± 5.2	25.6 ± 3.4	**<.001**
RER[l] at peak exercise	1.23 ± 0.09	1.24 ± 0.10	.320
Peak heart rate, bpm	167 ± 20	178 ± 14	**.006**
Peak systolic blood pressure, mmHg[m]	179 ± 29	187 ± 21	.186

[c]BMI: body mass index; [e]bpm: beats per minute; [n]CHD: congenital heart disease; [a]cm: centimeter; [b]kg: kilogram; [h]ln: natural logarithm; [j]ml/kg/min: milliliter per kilogram per minute; [m]mmHg: millimeter of mercury; [g]ms: milliseconds; [d]m²: square meter; [l]RER: respiratory exchange ratio; [f]RMSSD: root mean square of successive differences; [k]VE/VCO_2slope: slope of the minute ventilation and carbon dioxide production; [i]VO_2peak: oxygen uptake at peak exercise

*adjusted for sex, age and heart rate, mean ± standard deviation, significance value was set to ≤.05, highlighted in bold

Table 8: Comparison of patients with congenital heart disease according to diagnostic subgroups

	Left Heart Obstruction (n=51)	Right Heart Obstruction (n=68)	Transposition of the Great Arteries (n=31)	Fontan Circulation (n=29)	Miscellaneous (n=43)	Control Group (n=57)	p-value[#]
Anthropometrics							
Gender, female	16 (31.4%)	33 (48.5%)	10 (32.3%)	15 (51.7%)	23 (53.5%)	35 (61.4%)	**.017**
Age, years	29.9 ± 10.1	27.0 ± 11.4	27.1 ± 7.8	28.5 ± 7.3	29.5 ± 11.0	29.0 ± 7.1	.596
Height, cm[a]	173.7 ± 8.4	170.8 ± 9.2	173.6 ± 10.0	168.7 ± 9.4	169.8 ± 8.8	173.7 ± 8.6	.105
Weight, kg[b]	74.7 ± 15.1	66.9 ± 13.5	71.3 ± 14.2	64.7 ± 11.9	70.0 ± 14.5	67.7 ± 11.5	.364
BMI[c], kg/m^{2}[d]	24.7 ± 4.2	22.9 ± 4.1	23.6 ± 3.9	22.7 ± 3.3	24.2 ± 4.1	22.3 ± 2.6	**.006**
Autonomic Nervous System							
Heart rate, bpm[e]	71 ± 10	73 ± 11	71 ± 10	74 ± 12	76 ± 16	69 ± 10	**.021**
RMSSD[f], ms[g]	53.3 ± 36.9	46.8 ± 35.4	45.5 ± 32.0	26.8 ± 25.9	39.0 ± 25.2	65.3 ± 35.0	**<.001**
lnRMSSD[h], ms	3.77 ± 0.65	3.61 ± 0.70	3.56 ± 0.78	3.00 ± 0.77	3.43 ± 0.75	4.02 ± 0.59	**<.001**
lnRMSSD, ms (adjusted)*	3.74 ± 0.55	3.60 ± 0.54	3.49 ± 0.55	3.07 ± 0.54	3.61 ± 0.55	3.93 ± 0.55	**<.001**
Exercise Capacity							
VO_2peak[i], ml/kg/min[j]	30.5 ± 9.8	27.1 ± 8.0	28.2 ± 7.4	24.4 ± 6.3	26.1 ± 7.7	37.5 ± 8.1	**<.001**
VO_2predicted, %	86.8 ± 20.8	75.8 ± 17.1	77.2 ± 18.1	69.7 ± 13.1	79.1 ± 18.9	116.8 ± 24.7	**<.001**
VE/VCO_2slope[k]	25.5 ± 3.6	28.4 ± 4.6	26.8 ± 4.4	32.9 ± 4.0	29.4 ± 6.6	25.6 ± 3.4	**<.001**
RER[l] at peak exercise	1.21 ± 0.10	1.24 ± 0.10	1.24 ± 0.06	1.21 ± 0.08	1.22 ± 0.08	1.24 ± 0.10	.320
Peak heart rate, bpm	167 ± 19	169 ± 20	168 ± 21	161 ± 15	168 ± 20	178 ± 14	**.006**
Peak systolic blood pressure, mmHg[m]	183 ± 34	175 ± 27	184 ± 26	178 ± 29	178 ± 27	187 ± 21	.186

[c]BMI: body mass index; [e]bpm: beats per minute; [a]cm: centimeter; [b]kg: kilogram; [h]ln: natural logarithm; [j]ml/kg/min: milliliter per kilogram per minute; [m]mmHg: millimeter of mercury; [g]ms: milliseconds; [d]m^{2}: square meter; [l]RER: respiratory exchange ratio; [f]RMSSD: root mean square of successive differences; [k]VE/VCO_2slope: slope of the minute ventilation and carbon dioxide production; [i]VO_2peak: oxygen uptake at peak exercise

*adjusted for sex, age and heart rate, mean ± standard deviation

[#]analysis of variance for group comparison

5.3 Inspiratory Muscle Training did not Improve Exercise Capacity and Lung Function in Adult Patients with Fontan Circulation: a Randomized Controlled Trial

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Individual contribution:

I sampled the data of the spirometry and the CPET in the department of congenital heart disease and pediatric cardiology of the German Heart Centre Munich. I was responsible for the procurement of the required materials, randomization and explanation of the physiology of the respiratory system and the device's handling as well as for the illustration of the different breathing techniques. Additionally I conducted the weekly telephone supervision of all study patients. After data analysis I wrote the manuscript. Accordingly, I represent the main author of this paper and was mainly responsible for the submission.

All actions were taken in consultation with the co-authors, who supported me from the collection of the data to the completion of the paper. Prof. Dr. Alfred Hager was responsible for conception and design of the study and responsible for data monitoring and integrity. Prof. Dr. Renate Oberhoffer and Prof. Dr. Peter Ewert contributed to the design and conception of the study. All authors, but especially PD Dr. Jan Müller gave important input for revising and improving the quality of the manuscript.

Summary and main results:

The aims of the current study were to investigate the effect of a telephone-supervised, daily inspiratory muscle training (IMT) for six months on exercise capacity and on lung function in adult patients with Fontan circulation.

The study population of overall 42 adult patients with Fontan circulation (50% female; 30.5 ± 8.1 years) consisted of 9 patients who underwent APA, 8 who underwent AVA and 25 who underwent TCPC. During all study visits a lung function test and a CPET were performed according to recent guidelines. During the computerized spirometer test forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and the FEV_1/FVC ratio were

captured. Subsequently the incremental symptom-limited CPET was performed until exhaustion on an electronically braked bicycle ergometer in upright position. For the assessment of the exercise capacity, peak oxygen uptake ($\dot{V}O_2$peak) was calculated as the highest mean oxygen consumption obtained during any 30-second time interval. Additionally, saturation of peripheral oxygen and a 12-lead ECG were recorded during the entire examination and blood pressure measurements were taken every two minutes until termination of the test. After baseline evaluation patients were randomized either into an intervention group (IG, n=20) or control group (CG, n=22). From baseline evaluation until six months follow-up the IG performed a telephone-supervised daily IMT. During the IMT patients used an inspiratory resistive training device with individually adjustable load. Meanwhile, the CG continued their usual activities and started IMT under the same conditions after six months follow-up. To assess the sustainability of the training program, both groups were asked to continue performing IMT without weekly telephonic-supervision for another six months until the last re-evaluation.

After the first six months of IMT, both groups had not improved their $\dot{V}O_2$peak and $\dot{V}O_2$peak predicted ($\Delta\dot{V}O_2$peak: IG: 0.05 [-1.53; 1.33] ml/kg/min vs. CG: -0.50 [-1.20; 0.78] ml/kg/min; p=.784; $\Delta\dot{V}O_2$peak predicted: IG: 0.65 [-5.02; 5.95] % vs. CG: 0.08 [-3.84; 7.63] %; p=919), without any significant difference between IG and CG. Further no significant changes could be observed between the IG and the CG concerning ventilatory efficiency ($\Delta VE/VCO_2$slope: IG: 0.90 [-1.33; 3.33] vs. CG: 0.50 [-0.78; 2.00]; p=.740). At six months follow-up, no significant difference was found between the IG and the CG concerning FVC and FVC predicted (ΔFVC: IG: 0.07 [-0.16; 0.22] l vs. CG:-0.05 [-0.24; 0.18] l; p=.377; ΔFVC predicted: IG: 2.56 [-4.08; 5.74] % vs. -1.27 [-6.22; 3.69] %; p=.217). Additionally, FEV_1 and FEV_1 predicted did not change significantly after IMT between the IG and CG (ΔFEV_1: IG: 0.05 [-0.07; 0.13] l vs. CG: -0.10 [-0.19; 0.03] l; p=.082; ΔFEV_1: IG: 2.43 [-1.50; 3.88] % vs. CG: -2.38 [-5.16; 1.94] %; p=.072).

Adult patients with Fontan circulation showed impaired ventilatory function and exercise capacity in terms of a reduced forced vital capacity, forced expiratory volume in the first second and peak oxygen uptake, respectively. Nevertheless, this study did not show an improvement in exercise capacity or lung function after a weekly telephone-supervised, daily IMT for six months. According to current evidence, beneficial effects of IMT in adult patients with Fontan circulation cannot be verified. Nevertheless, oxygen saturation at rest improved

significantly, indicating either a reduction in chronic atelectasis or an enhancement of hypoxic pulmonary vasoconstriction resulting in an improvement in ventilation / perfusion matching.

Inspiratory Muscle Training did not Improve Exercise Capacity and Lung Function in Adult Patients with Fontan Circulation: a Randomized Controlled Trial

Abstract

Introduction: Patients with Fontan circulation have no sub-pulmonary ventricle and a passive pulmonary perfusion. Considerable percentage of the pulmonary blood flow is driven by pressure shift due to respiration. Impairments in respiratory musculature strength are associated with a reduced exercise capacity. This study investigated the effect of a daily six months inspiratory muscle training (IMT) on exercise and lung capacity in adult Fontan patients.

Patients and Methods: After a lung function and cardiopulmonary exercise test (CPET), 42 Fontan patients (50% female; 30.5 ± 8.1 years) were randomized either into an intervention group (IG) or a control group (CG). The IG performed a telephone-supervised, daily IMT of three sets with 10-30 repetitions for six months.

Results: After six months of IMT, the IG did not improve in any exercise and lung capacity parameter compared to CG. $\dot{V}O_2$peak ($\Delta\dot{V}O_2$peak: IG: 0.05 [-1.53; 1.33] ml/kg/min vs. CG: -0.50 [-1.20; 0.78] ml/kg/min; p=.784) and FVC (ΔFVC: IG: 0.07 [-0.16; 0.22] l vs. CG:-0.05 [-0.24; 0.18] l; p=.377) remained unchanged, while FEV_1 trended to improve (ΔFEV_1: IG: 0.05 [-0.07; 0.13] l vs. CG: -0.10 [-0.19; 0.03] l; p=.082). Only oxygen saturation at rest improved significantly (ΔSpO_2: IG: 1.50 [-0.25; 3.00] % vs. CG: -0.50 [-1.75; 0.75] %; p=.017).

Conclusion: A daily six months IMT did not improve exercise and lung capacity and lung volumes in Fontan patients.

Keywords: Fontan Operation, Exercise Capacity, Respiratory Muscle Training

Introduction

The Fontan procedure, which was first performed in the 70s, and its modification, the total cavopulmonary connection (TCPC) is nowadays still the most common palliative surgical procedure for patients with single ventricle anatomies, which are not suitable for biventricular repair.[43, 97, 247] In the course of surgery the systemic venous return is directly connected to the pulmonary arteries, without passing a sub-pulmonary ventricle.[129, 248] Due to these hemodynamic limitations of a missing sub-pulmonary chamber, pulmonary arterial and systemic venous blood flow are strongly affected by modest intrathoracic pressure shifts, since approximately 30% of flow in the systemic venous pathway is driven by respiration.[249, 250] In patients with Fontan circulation, blood flow in the inferior vena cava is increased during inspiration phase, enhancing the systemic venous blood return into the lungs considerably.[251, 252]

Young adults with severe congenital heart diseases (CHD), and Fontan circulation in particular, show respiratory and skeletal muscle weakness, and higher prevalence of respiratory muscle dysfunction, which are comparable to those of adults with advanced heart failure.[44] So the physiology of patients with Fontan circulation and patients with heart failure is partially coinciding. Both patient groups have impaired exercise capacity, reduced cardiac output, shallow and fast respiration.[227, 253] Furthermore, respiratory muscle weakness correlates well with reduced exercise capacity in these patients.[44, 45] Results of a meta-analysis and a systematic review show an increase in exercise capacity and an amelioration in dyspnea in patients with heart failure due to a respiratory muscle training which obtained improvements in respiratory muscle strength and endurance.[46, 47]

Also in a recent study in children with Fontan circulation a daily inspiratory muscle training (IMT) of six weeks improved inspiratory muscle strength and ventilatory efficiency in a cardiopulmonary exercise test (CPET).[254] Therefore it is reasonable that an individually adjusted IMT in adult patients with Fontan circulation improves parameters of ventilation and exercise capacity.

The aims of the current study were (1) to investigate the effect of a telephone-supervised, daily inspiratory muscle training for six months on exercise capacity and (2) on lung volumes in adult patients with Fontan circulation.

Patients and Methods

Study Subjects

Through databases of the Deutsches Herzzentrum München overall 656 adult patients with univentricular heart after palliative Fontan operation, were identified fulfilling the inclusion criteria (18 years and older, Fontan physiology), were identified (Figure 30). Patients who underwent cardiac catheter examination in the last six months or heart surgery in the last twelve months were excluded from the study. Further exclusion criteria were a change in drug administration in the last 3 months, planned intervention in the near future, neuromuscular mental disease, moderate to severe ventricular dysfunction as well as an instable general state of health. During initial medical consultation and examination five patients met the exclusion criteria and could not be included.

Therefore 42 patients (50% female; 30.5 ± 8.1 years; age 18 to 51 years old) out of 209 eligible patients participated in our study over the period from January 2017 until October 2018. 16 of our study patients were born with a tricuspid atresia, five with a double-outlet right ventricle (DORV), one with a double-inlet right ventricle (DIRV), 13 with a double-inlet left ventricle (DILV), two patients with a hypoplastic right ventricle and a transposition of the great arteries (TGA), three with hypoplastic right ventricle and a congenitally corrected transposition of the great arteries (ccTGA) and two patients with a single right ventricle and a complete atrioventricular septal defect (cAVSD). Consequently the study population exists of nine patients who underwent atriopulmonary anastomosis (APA), eight who underwent atrioventricular anastomosis (AVA) and 25 who underwent TCPC (Table 9).

After baseline assessments (visit 1), consisting of a lung function test (LFT) and a CPET, 42 patients were randomized either into an intervention group (IG, n=20) or control group (CG, n=22). The IG started performing a telephone-supervised, daily IMT until a six months follow-up (visit 2). The daily intervention was performed with an inspiratory resistive training device (POWERbreathe International Ltd., Southam, UK). Within the first six months after baseline evaluation the CG continued their usual activities and did not get any treatment. At the six months follow-up (visit 2) this group started IMT under the same conditions, including weekly telephone supervision till 12 months re-evaluation (visit 3). To assess the sustainability of the training program, the IG was asked to continue performing IMT without weekly telephonic-supervision until 12 months re-evaluation (visit 3). This independent six-months IMT period of the CG was performed from 12 months follow-up until 18 months re-evaluation (visit 4). The study consisted of three visits for the IG and four visits for the CG,

where a CPET and a LFT were performed, respectively. All tests were implemented by the same experienced sports scientist (C.F.).

A total of nine dropouts had to be registered during the whole study. In the CG two dropouts were recorded before the beginning of telephone-supervised intervention period. During intervention period four patients dropped out in both groups (IG: n=2; CG: n=2). Solely in the IG three further dropouts were registered after completion of supervised training period. Summarizing data from overall 38 study patients (IG: n=18; CG: n=20) were considered for randomized evaluation of IMT (Figure 30).

This study was a prospective, single-centre, randomized controlled trial. It was conducted in accordance with the Declaration of Helsinki (revision 2008) and the Good Clinical Practice guidelines. The study protocol was approved by the local ethical board (project number 52/14S) of the Technical University of Munich and registered in the DRKS.de website (registration ID: DRKS00010477). All participants gave a written informed consent and agreed to an anonymous publication of their data.

Inspiratory Muscle Training (IMT)

After baseline evaluation patients were instructed by an experienced sports scientist (C.F.) in term of the IMT. Physiology of the respiratory system and device's handling were explained, and different breathing techniques were illustrated and conducted with the patient. Patients were instructed to begin the inhalation phase with diaphragmatic breathing and to continue inhaling by expanding the rib cage. Incorrect breathing and malposition were corrected immediately.

Patients used an inspiratory resistive training device (POWERbreathe International Ltd., Southam, UK) for three sets with 10-30 repetitions once daily. The device's inspiratory load was adjusted individually until maximum for every training session to maintain an optimal training effect. During inhalation phase patients breathed towards an individually adjustable resistance, generated by varying the compression of a spring-loaded valve. An adjustment from 10 cm H_2O to 90 cm H_2O was possible. Accordingly, sufficient vacuum pressure needed to be generated during inspiration. Exhalation phase was unloaded.

To be able to support the patients, clarifying questions and assess compliance, the first six months training period was telephone-supervised weekly, since the training sessions were performed at home. During the second six months training period, patients were instructed to continue the IMT independently, since no telephone-supervision was implemented. Both

groups performed IMT under the same conditions. While the IG started with the telephone-supervised training session subsequent to baseline evaluation, no training was undertaken by the CG. Latter started with the first training period under telephone supervision subsequent to six months follow-up and continued with the second training period after 12 months re-evaluation (Figure 30).

Measurement of Exercise Capacity

Incremental symptom-limited CPET until exhaustion on an electronically braked bicycle ergometer was performed in upright position according to recent guidelines.[26] To define the baseline, a 3-minute rest period was observed. Following a 3-minute warm-up period without load, a ramp wise increase of load with 10, 15, 20 or 30 watts per minute was set. To determine each subject's limit of tolerance within 8 to 12 minutes after warm-up, the load increase was adjusted individually, based on the expected exercise capacity estimated by the investigator. Subsequent to exhaustion, a 5-minute recovery period proceeded, consisting of an initial cycling phase with minimal load for 2 minutes and an adjacent resting phase lasting for three minutes. Throughout testing patients complied with pedaling at a cadence between 60-80 revolutions per minute and were encouraged verbally to achieve maximal exhaustion.

Gas exchange and ventilation were measured via a breath-by-breath gas exchange analysis (Encore, SensorMedics, Viasys Healthcare, Yorba Linda, California, USA). During the entire examination saturation of peripheral oxygen and a 12-lead ECG were recorded. Furthermore, blood pressure measurements were taken every two minutes. Peak oxygen uptake ($\dot{V}O_2$peak) was calculated as the highest mean oxygen consumption obtained during any 30-second time interval. Reference values for gender, age, body height, and body mass, expressed in ''% predicted'' were calculated as previously described. Reference values for peak heart rate were calculated 208 - 0.7 x age according to Tanaka and colleagues.[231, 232] Compliance criteria for a valid CPET were achieved when either respiratory exchange ratio (RER) was ≥1.05, or peak heart rate was ≥85%. Cyanotic patients (oxygen saturation <90% at rest or at peak exercise) were rarely able to reach the above mentioned thresholds, however they were included in the study, independent of those criteria.[233, 234]

Measurement of Lung Function

Prior CPET forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and the FEV_1/FVC ratio were performed in a computerized spirometer test (Encore, SensorMedics, Viasys Healthcare, Yorba Linda, California, USA) in a seated upright position according to recent standardization of spirometry.[179] During the measurement patients utilized a nose clip and mouthpiece. Every patient performed at least three technically acceptable trials, while the best value was recorded to determine the degree of airflow. To ensure the reproducibility of the test, the two best values should not differ more than 5%.[179] Lung function measurements are expressed in liters and as percentage of the predicted values, corrected for gender, height, age and weight according to Pellegrino and colleagues.[192]

Data analysis

The Kolmogorov-Smirnov test failed to show normality in the primary outcome parameter peak oxygen uptake and other variables. Therefore, all descriptive data were shown in median and interquartile [IQR 25; 75] range. Pre-treatment and post-treatment data from the IG were compared to the data from the CG with a Wilcoxon rank sum test (Δ). Mann-Whitney U-Test was used to compare the differences between IG and CG. Sample size calculation was performed with the assumption to increase peak oxygen uptake by 3ml/kg/min due to the intervention. With an 80% power, α=5% and a dropout rate of 20% the minimum number of 40 patients was estimated.

All analyzes were performed using SPSS (version 23.0, IBM Corporation, Armonk, NY, USA) and a two-tailed probability value <.05 was considered statistically significant for all tests.

Results

Study characteristics of the patients with Fontan circulation of both groups are displayed in detail in Table 9.

Exercise Capacity

At six months re-evaluation both groups had not improved their $\dot{V}O_2$peak and $\dot{V}O_2$peak predicted ($\Delta\dot{V}O_2$peak: IG: 0.05 [-1.53; 1.33] ml/kg/min vs. CG: -0.50 [-1.20; 0.78] ml/kg/min; p=.784; $\Delta\dot{V}O_2$peak predicted: IG: 0.65 [-5.02; 5.95] % vs. CG: 0.08 [-3.84; 7.63] %; p=919), without any significant difference between IG and CG. Additionally no significant difference

was found between the IG and the CG concerning ventilatory efficiency ($\Delta VE/VCO_2$slope: IG: 0.90 [-1.33; 3.33] vs. CG: 0.50 [-0.78; 2.00]; p=.740).

The only significant result was an increase of oxygen saturation at rest in the IG in comparison to the CG (ΔSpO_2: IG: 1.50 [-0.25; 3.00] % vs. CG: -0.50 [-1.75; 0.75] %; p=.017) after six months IMT. Detailed overview of the parameters of exercise capacity after the randomized phase is demonstrated in Table 10.

Lung Function

After six months of IMT, no significant changes could be observed between the IG and the CG concerning FVC and FVC predicted (ΔFVC: IG: 0.07 [-0.16; 0.22] l vs. CG:-0.05 [-0.24; 0.18] l; p=.377; ΔFVC predicted: IG: 2.56 [-4.08; 5.74] % vs. -1.27 [-6.22; 3.69] %; p=.217). Further, FEV_1 and FEV_1 predicted did not change significantly after IMT between the IG and CG (ΔFEV_1: IG: 0.05 [-0.07; 0.13] l vs. CG: -0.10 [-0.19; 0.03] l; p=.082; ΔFEV_1: IG: 2.43 [-1.50; 3.88] % vs. CG: -2.38 [-5.16; 1.94] %; p=.072). Detailed overview of the lung values is demonstrated in Table 10.

Side Effects

In three study patients atrial flutter was already diagnosed and appeared during the study. In two of these patients atrial flatter could be terminated by electrical cardioversion. In one patient a cardiovascular ablation was performed resulting in a sinus arrest and an uneventful pacemaker implantation. The above-mentioned serious adverse events occurred during the patient's training phase. Nevertheless, due to the patient's previous medical history implicating up to four cardioversions a year, these events were unlikely attributable to the IMT.

Another patient was diagnosed with a diaphragmatic axial hernia during post-intervention period. According to the patient's own statements no IMT was performed after the completion of the telephone-supervised training period. An association between the IMT and the appearance of the diaphragmatic axial hernia could be conceivable, since its onset could be provoked by the increased inspiratory pressure during the training phase.

Discussion

This study did not show an improvement in exercise capacity or lung function after a weekly telephone-supervised, daily IMT for six months.

There is sufficient evidence that exercise limitations in patients with Fontan circulation are due to reduced stroke volume that originates from insufficient preloading conditions. Apart from these cardiac conditions, pulmonary issues have to be considered.[42, 129, 255] Patients with Fontan circulation show restrictive ventilatory function in terms of reduced FVC and FEV_1.[43] In young patients with Fontan circulation reduced FVC is common and associated with impaired exercise capacity, since a low breathing reserve limits their exercise performance.[43, 256] In terms of a restricted compensation of ventilatory inefficiency, a low FVC was shown to be a stronger predictor for reduced exercise capacity than markers for ventricular dysfunction or ventricular morphology.[43] Therefore, exercise limitation may be traced not only to cardiovascular, but also to pulmonary factors, such as a low breathing reserve and an increased pulmonary vascular resistance.[42, 43]

Up to now two studies of IMT in patients with Fontan circulation were conducted. A significant improvement in maximal inspiratory pressure was observed in young patients with nonfenestrated extracardiac conduit by Laohachai due to daily six week IMT.[254] In contrast to the results in young patients with Fontan surgery, an increase in maximal inspiratory pressure after 12 weeks of IMT could not be observed in a small cohort of eleven adult patients with Fontan circulation by Wu et al..[257] In the current study we did not measure maximal inspiratory pressure. In the same cohort by Wu et al., no change in peak tidal volume was found.[257] Though, a significant higher peak work rate as well as a tendency to ameliorated ventilatory efficiency and increased exercise capacity could be identified in these patients. A significant enhancement of ventilatory efficiency during exercise was shown in young patients with Fontan circulation, maybe representing an improvement in ventilation / perfusion matching, whereas an increase in oxygen saturation or O_2 pulse could not be observed.[254]

There are two main differences in the current study and the study by Laohachai et al. concerning the training structure and duration of the IMT. The current cohort performed an IMT, consisting of 3 sets with 10-30 repetitions once a day, and started the training without inspiratory load on the device and increased it at their discretion until maximum. This procedure represents strength training, whereas the patients in the other study performed endurance training. These patients trained for 30 minutes a day and the load on the device was set to 30% of particular maximal inspiratory pressure being reached at baseline evaluation. At

first re-evaluation after three weeks, the load was adjusted to potential changes in maximal inspiratory pressure.[254] Total duration was six weeks, whereas patients of the current cohort trained for six months. Taking these facts into account it can be concluded that endurance training is superior to strength training, also in case of shorter duration.

Yet, three months of controlled respiratory training without any training device, improved $\dot{V}O_2$peak and endurance time during CPET in a small cohort of adolescent patients with Fontan circulation.[258] This respiratory training form is based on diaphragmatic respiration and increases negative intrathoracic pressure, due to higher depth of inspiration, and optimizes systemic venous return.[258] Hence the load does not play a predominant role in the improvement of exercise capacity by inspiratory muscle training. Comparing study patients of the cohorts mentioned above, $\dot{V}O_2$peak solely increased in young and adolescent patients with Fontan circulation, but not in adult patients. It can be assumed that an improvement in lung function resulting in increased exercise capacity in adult patients with Fontan circulation cannot be achieved by inspiratory muscle training.[254, 257, 258] The age of the patients, as well as the differences in surgery and its modifications, considering the fact of improvement in palliation and medical aftercare over the last years, need to be considered when comparing study results.

The association of lung function and exercise capacity was recently confirmed by Callegari et al., who reported a high impact of ventilatory function on exercise limitation and consequently on exercise capacity.[256] In patients with Fontan circulation higher FEV_1 values result in a better VE/VCO_2slope, indicating improvement in ventilatory function which may result in ameliorating systemic oxygen delivery.[256] Furthermore an increase in FEV_1 is not solely associated with a lower VE/VCO_2slope, but also with an improvement in oxygen saturation.[256]

In the current study oxygen saturation improved significantly after six months of IMT, without an increase in lung function or ventilatory efficiency. These results indicate an enhancement of hypoxic pulmonary vasoconstriction resulting in an improvement in ventilation / perfusion matching, which favors systemic oxygen delivery by the constriction of intrapulmonary arteries reacting to alveolar hypoxia.[259] Patients with Fontan circulation often suffer from reduced oxygen saturation, due to increased pulmonary vascular resistance, restraining hypoxic pulmonary vasoconstriction. Another plausible mechanism could be a reduction in chronic atelectasis following IMT. Hence IMT may improve blood flow of the

lungs.[259] Further research focussing primary on oxygen saturation are needed to make those claims.

Conclusion

Six months of weekly telephone-supervised, daily IMT could not improve exercise and lung capacity in adult patients with Fontan circulation. According to current evidence, beneficial effects of IMT in adult patients with Fontan circulation cannot be verified. Therefore, larger studies are warranted in order to gain more insight into the mechanisms of exercise training and the Fontan physiology.

Figure

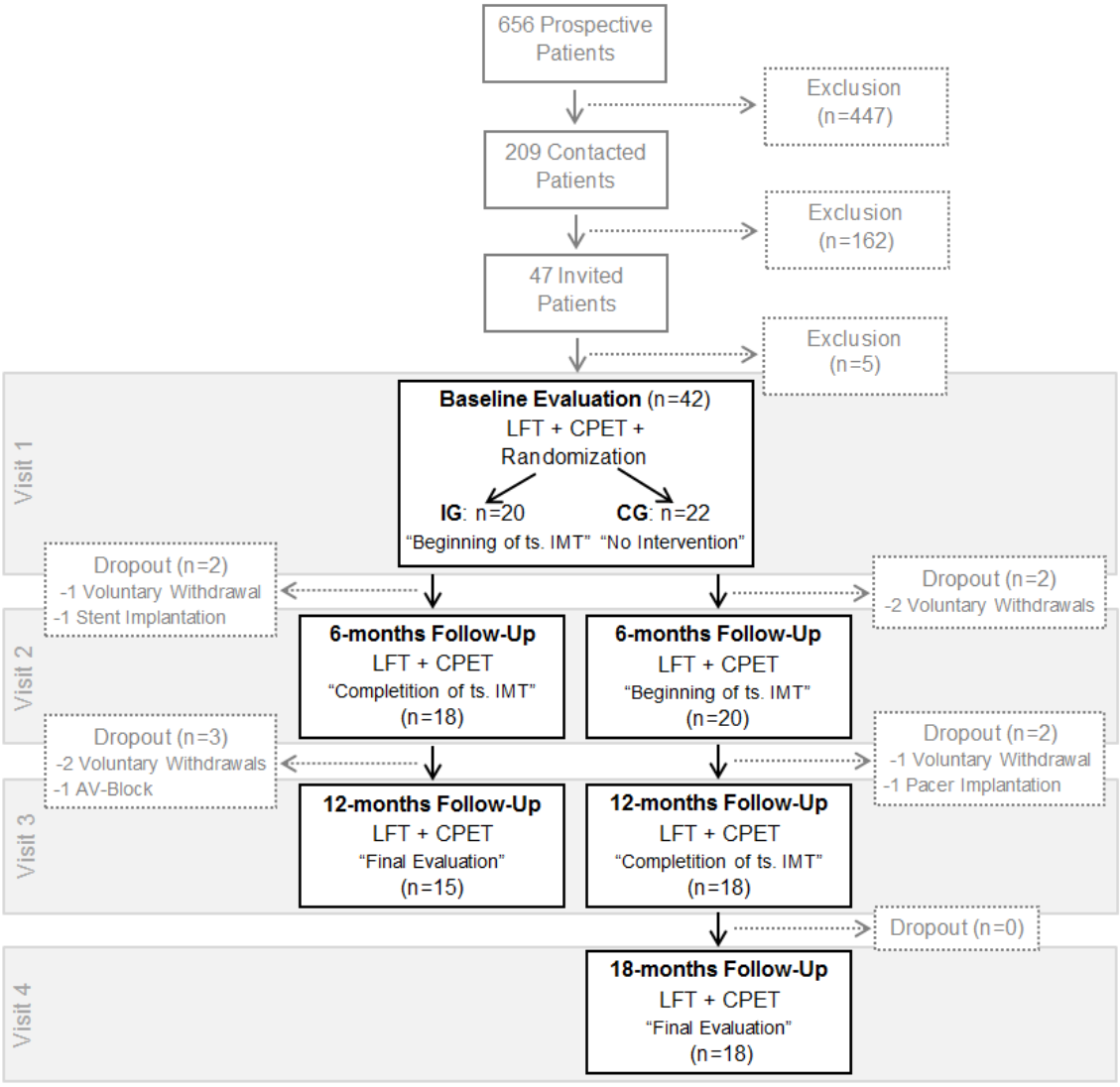

Figure 30: Course of study
CG: Control Group; CPET: Cardiopulmonary Exercise Test; IG: Intervention Group; LFT: Lung Function Test; ts. IMT: telephone-supervised Inspiratory Muscle Training

Tables

Table 9: Patients characteristics of study population

Patients Characteristics	Study Population (n=42)	Intervention Group (n=20)	Control Group (n=22)
Gender, female %	21 (50%)	9 (45%)	12 (55%)
Age, years	28.6 [24.7; 36.5]	28.8 [25.3; 38.3]	27.7 [23.7; 36.0]
Height, cm	170.0 [162.8; 177.5]	170.0 [163.5; 176.0]	170.5 [162.3; 178.5]
Weight, kg	67.0 [56.9; 78.0]	68.2 [58.8; 78.0]	66.3 [54.3; 78.3]
BMI, kg/m^2	22.0 [20.8; 26.2]	22.0 [21.3; 25.8]	22.6 [19.7; 26.5]
Age at Fontan Surgery, years	6.3 [4.0; 9.9]	6.2 [3.4; 7.8]	6.5 [4.1; 11.8]
Diagnosis			
Tricuspid Atresia	16	9	7
Double Outlet Right Ventricle	5	2	3
Double Inlet Right Ventricle	1	0	1
Double Inlet Left Ventricle	13	7	6
Transposition of the Great Arteries	2	1	1
congenitally corrected Transposition of the Great Arteries	3	0	3
Single Right Ventricle and a complete Atrioventricular Septal Defect	2	1	1
Ventricular morphology			
Left	36	18	18
Right	5	2	3
Indeterminate	1	0	1
Type of Palliation			
AVA	8	7	1
APA	9	3	6
TCPC	25	10	15
Medication			
Anticoagulation (oral)	33	16	17
Thrombosis inhibitor	5	1	4
Beta blocker	16	8	8
ACE inhibitor / AT inhibitor	10	7	3
Digitalis	1	0	1
Diuretic	7	2	5
PDE5 inhibitor	2	0	2
Antiarrhythmics	2	0	2
No medication	2	2	0

median and interquartile [IQR 25; 75]

cm: centimeter; kg: kilogram; BMI: body mass index; m²: square meter; AVA: Atrioventricular Anastomosis; APA: Atriopulmonary Anastomosis; TCPC: Total Cavopulmonary Connection; ACE: Angiotensin Converting Enzyme; AT: Angiotensin; PDE: Phosphodiesterase

Table 10: Mean differences between intervention group and control group after six months inspiratory muscle training

		Intervention Group (n=18)			Control Group (n=20)				
		Baseline Evaluation	6-Months Follow-Up	Difference	Baseline Evaluation	6-Months Follow-Up	Difference	Difference between IG and CG	p-value
Lung Function	FVC, l	3.8 [2.6; 4.9]	3.8 [2.8; 4.6]	0.07 [-0.16; 0.22]	3.6 [3.0; 4.3]	3.6 [2.9; 4.4]	-0.05 [-0.24; 0.18]	0.01 [-0.20; 0.20]	.377
	FVC predicted, %	85.4 [80.1; 96.8]	88.8 [80.4; 95.2]	2.56 [-4.08; 5.74]	87.8 [80.6; 97.6]	88.7 [76.5; 93.5]	-1.27 [-6.22; 3.69]	0.65 [-5.15; 4.72]	.217
	FEV_1, l	3.1 [2.2; 3.9]	3.0 [2.3; 3.7]	0.05 [-0.07; 0.13]	3.0 [2.5; 3.5]	3.0 [2.5; 3.4]	-0.10 [-0.19; 0.03]	-0.03 [-0.13; 0.08]	.082
	FEV_1 predicted, %	80.6 [74.3; 90.6]	81.4 [72.8; 88.5]	2.43 [-1.50; 3.88]	84.1 [78.9; 94.5]	83.4 [75.9; 91.6]	-2.38 [-5.16; 1.94]	0.03 [-3.33; 2.90]	.072
	FEV_1/FVC ratio, %	80.6 [77.8; 84.6]	77.7 [75.2; 84.0]	0.48 [-4.35; 2.40]	82.8 [80.6; 87.4]	81.5 [79.3; 84.9]	-0.88 [-3.71; 1.66]	-0.20 [-4.03; 2.03]	.460
Exercise Capacity	VO_2peak, ml/kg/min	23.4 [19.5; 28.5]	23.3 [19.1; 29.5]	0.05 [-1.53; 1.33]	24.1 [18.3; 27.7]	22.5 [18.0; 29.4]	-0.50 [-1.20; 0.78]	-0.23 [-1.36; 1.05]	.784
	VO_2 peak predicted, %	68.7 [64.3; 76.0]	70.1 [62.6; 80.0]	0.65 [-5.02; 5.95]	69.7 [55.6; 81.9]	67.3 [58.4; 80.1]	0.08 [-3.84; 7.63]	0.37 [-4.43; 6.79]	.919
	VE/VCO_2 slope	31.3 [27.5; 34.4]	31.4 [28.2; 35.2]	0.90 [-1.33; 3.33]	33.4 [30.0; 36.8]	33.5 [30.5; 36.7]	0.50 [-0.78; 2.00]	0.7 [-1.05; 2.66]	.740
	RER at peak exercise	1.24 [1.17; 1.3]	1.23 [1.15; 1.28]	0.01 [-0.08; 0.05]	1.24 [1.17; 1.28]	1.21 [1.18; 1.26]	0.00 [-0.05; 0.04]	0.00 [-0.07; 0.05]	.942
	Heart Rate max, bpm	148.5 [127.5; 173.0]	142.0 [136.8; 168.0]	-1.00 [-6.00; 3.00]	152.5 [148.0; 169.8]	158.5 [139.0; 167.3]	-2.50 [-6.75; 4.00]	-1.75 [-6.38; 3.50]	.718
	Blood Pressure max, mmHg	170.5 [155.3; 186.3]	174.0 [156.5; 191.0]	6.00 [-3.25; 17.25]	160.0 [150.5; 192.8]	172.5 [143.3; 200.3]	6.00 [-16.75; 23.75]	6.00 [-10.00; 20.50]	.740
	SpO_2 at rest, %	92.0 [89.0; 94.3]	93.5 [91.8; 96.0]	1.50 [-0.25; 3.00]	94.0 [88.5; 95.0]	93.5 [89.0; 95.0]	-0.50 [-1.75; 0.75]	0.50 [-1.00; 1.88]	**.017**
	SpO_2 at peak exercise, %	89.5 [84.0; 92.5]	90.0 [84.5; 93.5]	1.00 [-2.00; 3.00]	89.5 [84.5; 93.0]	90.5 [83.5; 93.0]	-0.50 [-2.00; 2.00]	0.48 [0.00; 2.50]	.517
	Watts max	158.0 [118.0; 201.3]	156.5 [116.8; 206.5]	0.00 [-10.50; 5.25]	133.0 [115.0; 201.50]	132.5 [108.5; 191.5]	-1.00 [-5.75; 2.00]	-0.50 [-8.13; 3.63]	.633

median and interquartile [IQR 25; 75], significance value was set to ≤.05, highlighted in bold

IG: Intervention Group; CG: Control Group; FVC: forced vital capacity; l: liter, FEV_1: forced expiratory volume in the first second; $\dot{V}O_2$peak: oxygen uptake at peak exercise; ml/kg/min: milliliter per kilogram per minute; VE/VCO_2slope: slope of the minute ventilation and carbon dioxide production; RER: respiratory exchange ratio; bpm: beats per minute; mmHg: millimeter of mercury; SpO_2: peripheral capillary oxygen saturation

6 Discussion

The purpose of this dissertation was to outline exercise capacity in the context of training, HRV and lung function in patients with CHD. In comparison to the general population, patients with CHD show decreased exercise capacity, lung function and a broad limitation of the ANS in previous studies.[7, 8, 12, 19, 29, 30, 38-41, 44, 45] These outcomes are associated with an increased risk of being affected by cardiovascular diseases, life-long comorbid conditions, diverse complications, hospitalization or death. The results of the current dissertation could confirm these earlier findings, indicating an impaired exercise capacity and regulation of the ANS in the majority of patients with CHD. Furthermore, especially patients with Fontan circulation show sympathovagal imbalance as well as a reduced exercise capacity and lung function. Individually adjusted exercise training programs seem essential for successfull CHD medical aftercare with the aim of improving health status and survival in this affected patient population.

The review examines the essential requirements for a safe recommendation on risk-free and effective exercise training in patients with CHD in accordance with recent guidelines.[16-20] It considers the requirements for both a detailed cardiac-specific examination and a successful integration of exercise training in the patient's daily life. Thus, the review combines interdisciplinary expertise from the fields of cardiology and sports science. This interdisciplinarity is prerequisite of a professional sport eligibility testing by the cardiologist and an established implementation in execution by the sports scientist, physiotherapist or trainer.

Since sport eligibility depends on the patient's risk that acute cardiac problems may occur, the aim of sport eligibility testing is the identification of residuals with a specific risk for disastrous events during physical activity.[211] Hence, cardiologists have to be familiar with the age-appropriate development of cardiopulmonary status, heart rhythm, exercise capacity, cardiac functionality and the hemodynamic significance of the residual findings.[196-203, 212] Additionally, the required equipment and personnel must be available in order to carry out the necessary investigations. A medical history should include a sport history.[212] Results of the CPET have to be carefully analyzed in order to give an appropriate sport recommendation to the patient. An additional cardiac magnetic resonance or a computed tomography scan might be necessary in certain patients.[212]

Furthermore, clinical considerations which are relevant to physical activity have to be observed. According to recent guidelines, the hemodynamic function and the unique clinical status have to be considered.[24, 212] Specialist knowledge about the initial CHD, its sequence of therapeutic interventions, the extent of the residual findings and the evaluation of the functions are prerequisite for a valid decision regarding the patient's individual risk.[212] Incorrect assessments could have disastrous consequences for the patient and his or her companion during physical activities, including dissection, arrhythmia and sudden cardiac death.[18, 24, 211] All these requirements must be fulfilled by the cardiologist in order to make a suitable recommendation, based on a successful sport eligibility test, without exposing the patient to any risk. Due to the lack of experience and expertise in the field of CHD or the absence of required equipment, the implementation of the sport eligibility testing outside ACHD centers is practically impossible.

In addition to the cardiovascular prerequisites, performance of the physical activity also needs to be considered for a goal-oriented recommendation regarding suitable sports. Sports and their respective movement pattern, intensity, impact and their influence on aerobic capacity, strength and flexibility have to be taken into account. Only a few cardiologists have the expertise about these facts and about underlying training principles and training methods. Furthermore, exercise training needs to be specifically tailored to the patient, discussing characteristics, such as previous physical inactivity, exercise experiences, preferences and training goals together with the patient.[212] In this context, the expertise and experience of the sports scientist is needed. However, sports scientists are usually not familiar with CHD, the associated hemodynamic significance of the residual findings, the cardiac functionality and the consequent exercise capacity. With regard to this issue, the interdisciplinary character of this review constitutes the interface between cardiology and sports science. The review provides cardiologists with practical advices, recommendations and prohibitions, taking specific clinical considerations such as ventricular dysfunction, aortic abnormalities, syncope, cyanosis, arrhythmia and device implantation into account.

The results of study II demonstrate that patients with CHD show impairments in parasympathetic activity in comparison to healthy controls. These results validate earlier findings indicating a broad limitation of the ANS, reflecting impaired parasympathetic activity, in the vast majority of patients with CHD.[38-40, 224] It is assumed that the sympathovagal imbalance is primarily caused by myocardial damage due to surgical intervention, involving scars and fibrotic tissue that may result in electrically unexcitable

regions.[225] The vast majority of affected patients has moderate or complex lesions. The current results can confirm the assumption, since the examination of heart defect severity shows an impaired parasympathetic activity in patients with complex CHD compared to the CG and to patients with mild and moderate CHD. Further, patients with moderate CHD show reduced parasympathetic activity in comparison to healthy controls.

So far, individual heart defects have predominantly been compared with a suitable CG, and statements on the comparison between the individual subgroups have rarely been made due to different measuring methods, as well as small and inhomogeneous subgroups. Based on the high sample size in the present study, it was possible to consider individual subgroups and to compare them with the CG and with each other. Within the present examination all subgroups, except patients with LHO, show a decreased parasympathetic activity. Patients with Fontan circulation have the most impaired sympathovagal imbalance. These results indicate that not all patients with CHD have the same manifestation of the limitation of the ANS, but that it is affected by the impacts of the respective CHD. This may be the reason why not all results of previous studies demonstrate an imbalance of the ANS.[260, 261] Patients with complex CHD, especially patients who underwent Fontan surgery, show the most sympathovagal imbalance, being associated with cardiac electrical instability, due to their surgical scars in the atria.[262] The current results confirm the statement that a limitation of the ANS represents an independent predictor of arrhythmic complications and cardiac death.[37, 221]

However, the strongest predictor of mortality and morbidity in patients with CHD is still exercise capacity.[27] This fact is of concern, since patients with CHD show not only limitations of the ANS, but also show a reduced peak oxygen uptake compared to healthy controls.[19, 30, 38-40, 224] The results of study II validate earlier findings showing a decreased peak oxygen uptake in patients with CHD. An association between exercise capacity and HRV has already been observed in healthy individuals.[28, 34] Besides, there is evidence that exercise training results in improved parasympathetic activity and exercise capacity in the general population.[28, 34] The novel character of this study is that parasympathetic activity is moderately associated with peak oxygen uptake. This finding has so far only been reported in patients with ToF.[245] There is reason to assume that exercise training could affect the imbalance of the ANS, increasing parasympathetic activity and exercise capacity, and therefore result in an improved health status and survival in patients with CHD. The regulation of the ANS is not solely influenced by exercise training. Also relaxation techniques including progressive muscle relaxation, mindfulness-based stress reduction and breathing

exercises can restore the balance of the ANS.[263-266] In particular, patients with moderate and complex CHD would benefit from these therapeutic interventions, considering the hemodynamic function and unique clinical status. Especially patients with Fontan circulation have hemodynamic limitations, based on a missing subpulmonary ventricle implicating a pulmonary blood flow which is driven by pressure shifts due to respiration.[249, 250]

The results of study III demonstrate that adult patients with Fontan circulation show impaired exercise capacity by means of decreased peak oxygen uptake. These results confirm the results from other studies showing a diminished exercise capacity in these patients in comparison to healthy individuals and to the vast majority of other patients with CHD.[19, 29, 30, 44, 45, 267] Peak oxygen uptake is defined by the Fick equation as the product of cardiac output and arteriovenous oxygen difference.[268] The unique characteristic of this patient group is the restricted blood flow return from the pulmonary vascular bed, resulting in an impaired preload reserve of the ventricle.[42] Accordingly, reasonable ventricular contractility, heart rate increase and reduction of afterload have almost no influence on controlling cardiac output.[42] There is evidence that cardiac output seems to be predominantly determined by preload, which in turn is predetermined by transpulmonary flow.[42, 269] Pulmonary vascular resistance appears to be the major determinant of cardiac output, while low resistance is associated with good circulatory output.[42] Therefore, also pulmonary factors influence exercise limitation.

Earlier findings demonstrate the association of impaired exercise capacity with respiratory muscle weakness and reduced FVC in patients with Fontan circulation, since a low breathing reserve limits their exercise performance.[43] The vast majority of these patients suffers from respiratory and skeletal muscle weakness, a higher prevalence of respiratory muscle dysfunction and restrictive ventilatory function.[43, 44, 256] The results of the current study validate the latter findings showing decreased FEV1 and FVC in the current study population.

Furthermore, the results of this study show that exercise and lung capacity in adult patients with Fontan circulation could not be improved due to six months telephone-supervised, daily IMT. So far only two studies regarding IMT in Fontan patients have been published with different results.[254, 257] One study reported an increased maximal inspiratory pressure and a reduced VE/VCO_2slope in adolescent Fontan patients, whereas the other study exclusively found an improvement in peak work rate.[254, 257] Maximal inspiratory pressure had not been captured in the current study and a change of this parameter could not be observed by the second study.[257] A decreased VE/VCO2slope or an increased peak work rate could neither be found in the current study nor confirmed by the other study.[254] In both IMT studies $\dot{V}O_2$peak,

FVC and FEV1 did not increase.[254, 257] These results could be validated by the current results. In contrast an improvement of $\dot{V}O_2$peak and endurance time during CPET could be achieved on the basis of controlled respiratory training without any training device in a small cohort of adolescent patients with Fontan circulation.[258]

To the best of our knowledge study III is the first randomized controlled trial having examined the effects of an IMT in adult patients with Fontan circulation. In addition, a comparison of this sample size with those of the other studies shows a clear superiority of the current study. An improvement in muscle strength and exercise capacity could only be achieved in adolescent patients with Fontan circulation, but not in adult patients.[254, 257, 258] Not only the age, but the differences in surgery and its modifications, considering the fact of improvement in palliation and medical aftercare over the last years, need to be considered. Due to the large sample size in the current study, it can be assumed that an improvement in lung function and exercise capacity cannot be achieved in adult patients with Fontan circulation by IMT.

6.1 Limitations of the current research

The review is based on the recent guidelines and constitutes the interface between cardiology and sports science, providing cardiologists with practical advices, recommendations and prohibitions. Nevertheless, the superficial presentation of sports and their respective movement pattern, intensity, impact and their influence on aerobic capacity, strength and flexibility is not sufficient to provide detailed expert knowledge giving them the confidence to make appropriate and risk-free recommendations. Patients who suffer from hereditary disease or additional comorbidities like obesity, diabetes or orthopedic illnesses were not taken into account when recommendations were made.

In study II the CG does not match the patients with CHD perfectly, as the BMI is 1.3 kg/m^2 lower and the proportion of women in the CG is 16.9% higher than in the patients group. Latter is one of the factors influencing HRV, but gender only has a minor influence. Compared to the other subgroups, two of the five subgroups are quite small. This fact may be due to the underlying heart defects as they have a lower prevalence compared to the other heart defects. Nevertheless, the large sample size is sufficient to allow conclusions to be drawn regarding the regulation of the ANS concerning subgroups. A total of 130 adjacent heartbeats were recorded during the HRV measurement in supine position. Thus, the measurement is classified as a short-term measurement. HRV was almost exclusively detected

from long-term measurements in the other studies. According to the recent guidelines, it is inappropriate to compare measures from recordings capturing the parasympathetic activity of different durations.[156] HRV can be evaluated by a number of methods, such as time domain measures and frequency domain measures. While in the present study parameters of the time domain measurements were recorded, in almost all other studies parameters of the frequency domain analysis were captured. Even if, according to the guidelines, the results of both analyses are equivalent, a comparison of the results is not easily possible without additional effort.[156] Regarding the exercise capacity, a correlation could be observed. No direct influence of exercise training on HRV could be determined, due to the cross sectional study design.

In study III the patients with Fontan circulation were instructed on the IMT and the underlying physiology of the respiratory system. Furthermore, they received information on the handling of the training device as well as illustration and conduction of different breathing techniques. However, execution of the breathing techniques of these patients was not monitored during training period and slight mistakes in movement execution could have developed over time. The other two currently existing IMT studies also had no monitoring of the movement execution.[254, 257] Nevertheless, one study reviewed the training technique after half of the entire six-week training period. In this time, these patients underwent endurance training with duration of 30 minutes per training session and the inspiratory load on the device was set to 30% of the measured maximal inspiratory pressure.[254] In the current study maximal inspiratory pressure had not been captured during lung function test. The patients of this study performed strength training of the diaphragm and intercostal musculature during daily training sessions. The inspiratory load was adjusted individually by the patients and it was not verified during six months training period. Therefore, it could have been possible that some patients had trained just under submaximal load, leading to a reduced impact on muscle development and muscle strength.

Both in the current study and in the other IMT studies, the intervention consisted exclusively of IMT.[254, 257] The Fontan patients' reduced lung function may be due to respiratory muscle weakness, restricted chest wall or diaphragmatic palsy as a result of previous surgical interventions.[191] Therefore, an improvement of lung function could not be achieved by IMT alone. Limitations in skeletal muscles function could also be a factor explaining reduced exercise performance in these patients.[191] Although pulmonary vascular resistance influences exercise capacity in patients with Fontan circulation, this parameter was not recorded in the

current study and in the other IMT studies.[42] Blood flow in the inferior vena cava is increased during inspiration phase, enhancing the systemic venous blood return into the lungs considerably.[251, 252] Hence, an IMT could reduce pulmonary vascular resistance and thus improve circulatory output and long-term outcome in these patients.

6.2 Research perspectives

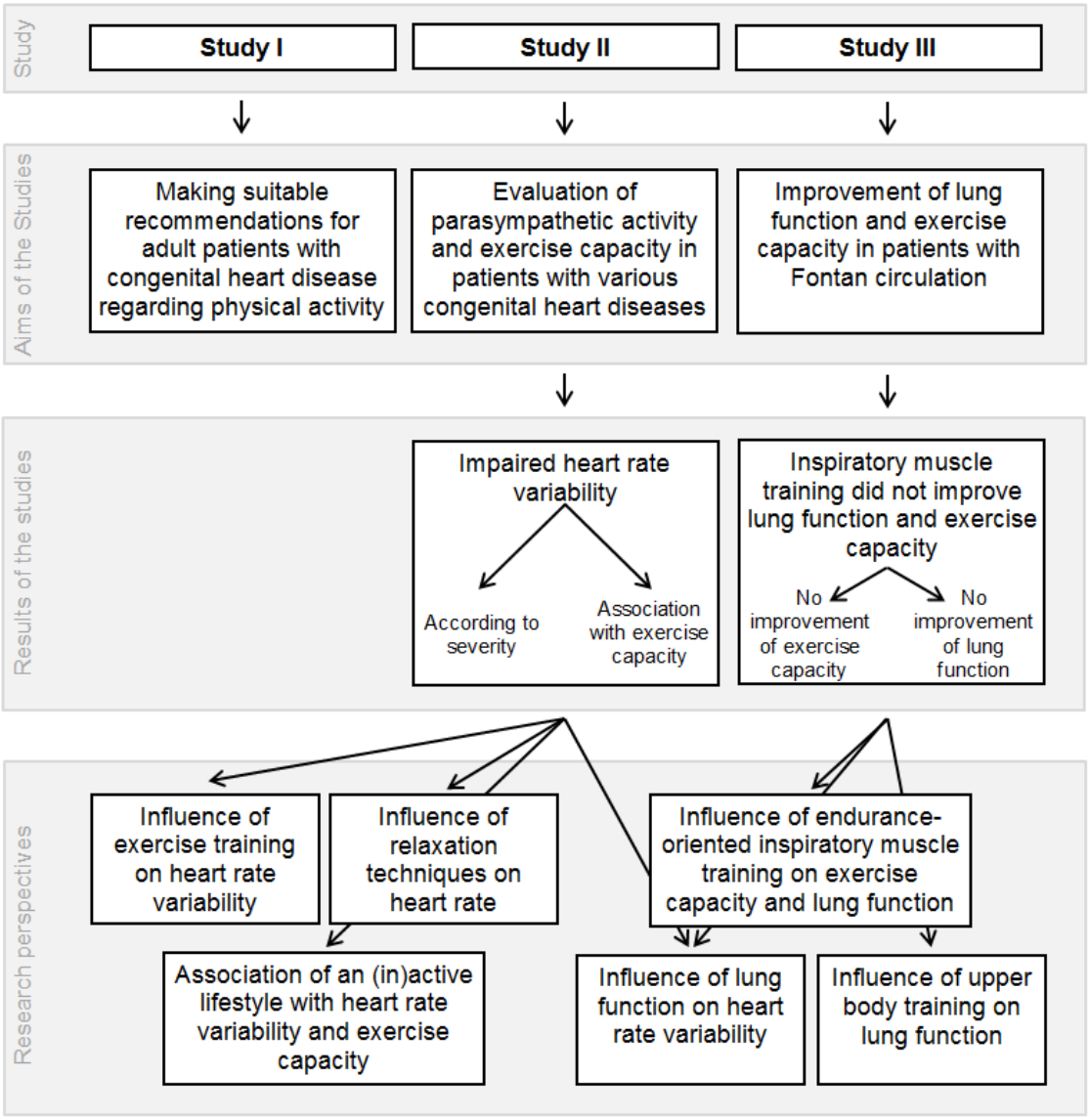

Figure 31: Research perspectives

6.2.1 Influence of exercise training on heart rate variability

There is agreement that an increase in exercise capacity is associated with an improvement in parasympathetic activity in the general population as well as in elderly people and patients with COPD and hypertension.[28, 34, 270-273] The results of study II show for the first time that exercise capacity is associated with parasympathetic activity in patients with different types of CHD. To the best of my knowledge, so far there is only one other study that evaluated the association between exercise capacity and HRV in 30 patients with ToF.[245] In both studies no intervention took place. It is not yet possible to say whether an improvement in exercise

capacity will be accompanied by a decreased limitation of the ANS in patients with CHD. However, results from numerous studies indicate an improved regulation of the ANS in athletes compared to matched sedentary individuals.[274-278] Additionally it is assumed that aerobic exercise training may be a useful alternative or adjunct to drug therapy in lessening the derangements of autonomic balance in many cardiovascular diseases.[274] Therefore future studies should evaluate the influence of exercise capacity on HRV in patients with CHD in comparison to a CG, continuing its usual activities. Taking the research results for healthy people and the recommendations for physical activity according to recent guidelines into account, endurance training in form of a randomized controlled trial would be desirable for patients with CHD. To consider heart defect severity, subgroups or even individual type of defect, a large study population, based on sample size calculation, would be preferable. To evaluate the training effect of tailored endurance training, a CPET and HRV measurement should be performed during both the baseline evaluation and follow-up. A period of approximately three months should elapse before re-evaluation in order to check the extent to which the patients were able to integrate the training into their daily routines. In addition, I recommend keeping a training diary for future research studies.

6.2.2 Influence of relaxation techniques on heart rate variability

The results of study II confirm results of previous studies implicating a limitation of the ANS by means of reduced parasympathetic activity in most patients with CHD.[38-40, 224, 225] There is agreement that relaxation techniques achieve an increase of parasympathetic and a decrease of sympathetic activity in healthy individuals as well as in men after post-myocardial infarction stenting.[263-266]

Yoga includes diverse practices, for instance regulated breathing, physical postures, meditation and instructed relaxation.[264] Numerous studies confirm a positive shift in the autonomic balance, implicating a significant increase of the parasympathetic and a significant decrease of the sympathetic activity, regardless of the different yoga relaxation techniques.[263-265] Mindfulness-based stress reduction, which is a meditation training shifting the minds focus to various parts of the body and the breathing, and progressive muscle relaxation, a classic relaxation technique involving tensing and relaxation of different muscle groups, also improve regulation of the ANS in men after post-myocardial infarction stenting.[266] Therefore, I recommend conducting studies evaluating the influence of relaxation techniques on HRV in patients with CHD. These techniques should be performed under the guidance of a respective

specialist, ensuring that the techniques are implemented correctly. The sessions should take place several times a week and comprise a total of at least 20 hours. HRV should be recorded before, during and after the first and last session. A randomized controlled trial evaluating different relaxation techniques, based on sample size calculation, and a CG not receiving intervention would be desirable.

6.2.3 Association of an (in)active lifestyle with heart rate variability and exercise capacity

It is known that physical inactivity is one of the biggest health hazards in our society.[22] Most patients with CHD have a more sedentary lifestyle compared to the general population and do not participate in regular exercise programs.[23, 24] Furthermore, the results of study II confirm results of previous studies implicating that patients with CHD show a limitation of the ANS and a reduced exercise capacity.[19, 29, 30, 38-40, 224, 225] The evaluation of daily activity, HRV and exercise capacity can reveal if there is an association of (in)activity with HRV and exercise capacity and if an active lifestyle involves increased HRV and exercise capacity.

Therefore, I recommend to conduct an intervention-free study including two evaluations, each with one long-term ECG Holter monitoring and a wearable the day before evaluation. The ECG device should be capable of detecting HRV. On the morning before baseline evaluation 24 hour monitoring and a wearable should be distributed to the patient. To capture everyday activity wearables recording among others the number of steps, covered kilometers, calorie consumption and heart rate could be used. If a wearable that can also record HRV is used, wearing the ECG device at the same time verifies the HRV measurement of the wearable. I also recommend distributing the wearable simultaneously with the ECG device, in order to record the activity level. This would be interesting knowledge as for example inactivity or physical activities can significantly influence HRV both during exercise and recovery time. At baseline evaluation a CPET should be performed in order to determine exercise capacity. Patients should wear their wearables for three months and continue their usual activities. After this time period follow-up evaluation should be carried out. Again long-term ECG Holter monitoring to evaluate HRV independently of the CPET should be done the day before. The follow-up should serve as a re-evaluation of HRV and exercise capacity. The recording of the 3-month activity using wearables should be sufficient to obtain statements about the patient's lifestyle and to find out if there is an association of (in)activity with HRV and exercise capacity. Since study results have shown that a change in motivation over a period of 8

months can be detected by wearables, the data provided after 3 months should realistically represent the daily activity of patients with CHD.[279] If the wearables could record the HRV, the daily HRV of the three months could additionally be evaluated. Furthermore, this time span should also be sufficient to capture possible non-scheduled changes in HRV and capacity. An additional comparison with healthy individuals would be desirable to assess if patients with CHD have impaired HRV and exercise capacity at the same activity level. Further, the study could be improved through a subgroup comparison.

This intervention-free study could also be converted into an intervention study including exercise training and / or relaxation techniques in order to examine the regulation of the ANS and exercise capacity.

6.2.4 Influence of endurance-oriented inspiratory muscle training on exercise capacity and lung function

The results of study III confirm results of previous studies implicating an impaired exercise capacity and lung function in patients with Fontan circulation.[19, 29, 30, 43-45, 256, 267] These patients show respiratory and skeletal muscle weakness and higher prevalence of respiratory muscle dysfunction, being associated with a reduced exercise capacity.[43, 44, 256, 280] Further, results of a meta-analysis and a systematic review show an increase in exercise capacity in patients with heart failure, due to a respiratory muscle training which obtained improvements in respiratory muscle strength and endurance.[44, 46, 47] The heart failure patients' physiology is partially coinciding with Fontan physiology.[227, 253] So far, two studies have evaluated IMT in patients with Fontan circulation.[254, 257] These studies and the current study have not achieved an improvement in lung function.[254, 257] Nevertheless, IMT in patients with Fontan circulation seems reasonable, since in these patients blood flow in the inferior vena cava is increased during inspiration phase, considerably enhancing the systemic venous blood return into the lungs.[251, 252] Further, inspiration involves active contraction of the muscles, while expiration is a passive process. Furthermore the three studies achieved different results concerning the improvement of exercise capacity.[254, 257]

The methods of these studies differ with regard to the intervention period, the execution of the training and the recorded parameters of lung function.[254, 257] Taking into account the different methodology and achieved results, future studies should investigate endurance-oriented IMT, which also contains theoretical and practical content on anatomy and physiology of the respiratory system as well as breathing control and breathing awareness. CPET and lung

function should be performed during baseline evaluation and follow-ups. During lung function test, the maximal inspiratory pressure should be detected in order to adjust the training load objectively. Patients should attend theoretical and practical sessions under the guidance of a specialist on a weekly basis in order to ensure optimal execution of the IMT and increase their attention. The IMT should be performed 30 minutes daily for a period of at least 8 weeks. A randomized trial, based on sample size calculation, would be ideal to evaluate the influence of an endurance-oriented IMT on lung function and exercise capacity in patients with Fontan circulation. A training diary and a six-minute walk test before the CPET as well as evaluation of pulmonary vascular resistance would also be preferable to further improve findings on the subject matter.

6.2.5 Influence of upper body training on lung function

Lung function is not exclusively dependent on the respiratory muscle strength. A restricted chest wall or diaphragmatic palsy due to surgical interventions may also contribute to a reduced lung function in patients with Fontan circulation.[191] Since IMT exclusively targets to train diaphragm and intercostal musculature, an improvement of lung function cannot be achieved by this training method alone in these patients. Since study results show an association of muscle strength and lung function, an additional increase in the flexibility and muscle strength of the upper body would be useful.[281]

Therefore, future studies should evaluate the influence of upper body training on lung function in patients with Fontan circulation. I recommend the execution of the upper body training, including flexibility and strength training. During the baseline evaluation and re-evaluation, flexibility tests and maximum strength tests of the upper body and upper extremities as well as a lung function test should be performed. Subsequently, training contents should be discussed theoretically and also carried out practically with a specialist. In these patients, especially during strength training and maximum strength tests, care must be taken that no Valsalva maneuver is induced in order not to block the circulation in the lungs. Training should be performed three times a week for a period of at least 2 months. To ensure correct implementation of training techniques, one training session should be performed under the guidance of the specialist four weeks after baseline evaluation. I recommend keeping a diary to review and reconstruct execution and progress of the training. A randomized controlled trial, based on sample size calculation, and a CG not receiving intervention would

be preferable to evaluate the influence of upper body training on lung function in patients with Fontan circulation.

In addition, an intervention study can be designed dealing with both the influence of endurance-oriented IMT and the influence of upper body training. Therefore, I recommend three IG and one CG, continuing usual activities. Two groups should receive endurance-oriented IMT or upper body training respectively and one group should receive both interventions. To evaluate whether these interventions also affect exercise capacity, CPET could be performed during baseline evaluation and follow-up.

6.2.6 Influence of lung function on heart rate variability

There is agreement on the association of lung function with HRV in healthy adults, smokers, patients with chronic obstructive pulmonary disease and patients with chronic spinal cord injury.[282-286] Nevertheless, current evidence is quite scarce. In patients with CHD the relationship between lung function and HRV is unclear, since there are only few studies evaluating this association. In spite of that, current literature indicates a positive correlation between these two parameters in healthy adults.[283, 284] Compared to healthy people, smokers show significantly impaired lung function and HRV.[282] However, poor HRV in smokers may also be attributable to other factors than an impaired lung function. Further, reduced HRV was also observed in patients with chronic obstructive pulmonary disease.[285] Individuals with chronic spinal cord injury show significantly increased FVC, FEV_1, HRV as well as cardiovascular response during orthostatic stress test after pressure threshold respiratory training.[286] Moreover, respiratory function and regulation of the ANS could be improved due to respiratory yoga training in healthy elderly subjects.[283] Hence, results from previous studies indicate an increase of sympathovagal balance due to improvement in lung function by use of different training methods in healthy elderly subjects and in patients with chronic spinal cord injury.[283, 286]

The results of both current studies show that patients with Fontan circulation suffer from impaired lung function and regulation of the ANS. Therefore future studies should evaluate the influence of lung function on HRV in these patients. A randomized controlled trial, based on sample size calculation, and a CG continuing its usual activities would be desirable. During both, baseline and follow-up evaluation a lung function test and a HRV measurement should be performed to evaluate the training effects of different respiratory training methods and their influence on HRV. Patients should keep a training diary and attend theoretical and

practical sessions under the guidance of a specialist in order to ensure optimal execution at least once or even more often between these evaluations, depending on the training method.

7 Conclusions and implications

Based on the findings of this dissertation, it can be concluded that exercise capacity, HRV and lung function are impaired in patients with CHD, especially in Fontan patients, and that individually adjusted exercise training is a determinant factor influencing health status and survival in these patients. The results show impaired exercise capacity and a limitation of the ANS in patients with CHD, which seem to be moderately associated. Furthermore, evidence regarding the influence of severity and individual subgroups of the heart defects on HRV and an existing association between peak oxygen uptake and parasympathetic activity could be provided. Especially patients with Fontan circulation suffer from sympathovagal imbalance and show impaired exercise capacity and lung function.

I strongly recommend evaluating whether exercise training, relaxation techniques and the improvement of lung function can influence HRV in patients with CHD.[37, 221] Respective interventions should aim to improve the regulation of the ANS being associated with a positive shift in the autonomic balance, implicating a significant increase of the parasympathetic and a significant decrease of the sympathetic activity. Based on these results therapeutic options improving sympathovagal balance, exercise capacity and therefore health status and survival in patients with CHD are suggested. Patients who underwent Fontan surgery show impaired exercise capacity and ventilatory function that could not be improved due to six months telephone-supervised, daily IMT. There is an urgent need for research in this field, as results of the few current studies do not coincide. I recommend examining the influence of an endurance-oriented IMT on lung function and exercise capacity. Investigations determining whether flexibility training and strength training of the upper body and upper extremities have an effect on lung function should also be conducted.

Exercise training in patients with CHD should only be performed after sport eligibility testing, consultation with the cardiologist and in accordance with recent guidelines. Recent diagnostic findings, medication, and patient's requests and expectations should be considered when recommending individually adjusted exercise trainings and physical activities, thereby enabling patients with CHD risk-free physical activities providing pleasure and improving health status. The extension of interdisciplinarity between cardiologists and sports scientists is desirable, since the combination of the expertise of both fields can lead to the best possible results for patients with CHD. Based on considerations resulting from this dissertation, interventions should aim at improving patients exercise capacity in the long term. Particular attention should be paid to patients with complex severity, especially patients with Fontan

circulation, as it has been confirmed that these patients are most impaired and therefore would benefit to a greater extend from interventions than patients with simple or moderate severity.

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Thank you all!

9 References

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10 Appendix

Appendix A

Klinik für Kinderkardiologie und
angeborene Herzfehler

Direktor: Prof. Dr. med. P. Ewert

Deutsches Herzzentrum München
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- Klinik an der Technischen Universität München -

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PATIENTENINFORMATION

zur Studie

Atemtraining bei Patienten mit univentrikulärem Herzen

nach palliativer Fontan-Operation

Sehr geehrte Patientin, sehr geehrter Patient!

Sie haben einen angeborenen Herzfehler, der mit einer Fontan-Operation behandelt werden konnte. Ein normales, gesundes Herz verfügt über zwei Herzkammern. Die linke Herzkammer pumpt sauerstoffreiches Blut in die Körperschlagader und die rechte Herzkammer das verbrauchte sauerstoffarme Blut in die Lunge.

Es gibt Patienten, die wegen ihres Herzfehlers nur eine funktionsfähige Herzkammer besitzen, ein sogenanntes univentrikuläres Herz. In diesem univentrikulären Herz wird sowohl die Körper- als auch die Lungenschlagader aus derselben Herzkammer versorgt. Dadurch vermischt sich sauerstoffarmes und sauerstoffreiches Blut. Die gesamte Sauerstoffsättigung im Körper wird in Folge geringer. Im Säuglings- und Kleinkindalter kann man nach 1-2 Voroperationen mit einer Operation, deren Details sich im Laufe der Zeit geringfügig geändert haben, einen Fontan Kreislauf erstellen. Ziel ist die Normalisierung der Blutströmung zu einem möglichst frühen Zeitpunkt. Mit Hilfe dieser Operation wird gewährleistet, dass das sauerstoffarme Blut zuerst in der Lunge mit Sauerstoff angereichert wird, bevor es zurück zum Herzen gelangen und in der Folge den Körper mit Sauerstoff versorgen kann. Ein direkter Anschluss der Hohlvenen an die Lungenschlagader ermöglicht den Transport des sauerstoffarmen Blutes aus dem Körper zur Lunge. Somit steigt nach dieser Operation die gesamte Sauerstoffsättigung im Körper. Diese Korrektur wird als palliative Operation bezeichnet, da zwar funktionell der Lungen- und Körperkreislauf wieder hergestellt wird, jedoch die Herzkammer zur Unterstützung des Lungenkreislaufes fehlt. Ergebnisse zeigen, dass die

Lebenserwartung durch diese operativen Maßnahmen deutlich gestiegen ist. Auf Grund dieser Tatsache wendet sich das Augenmerk der Forschung nun auf die Verbesserung Ihres Allgemeinzustandes, Ihrer Leistungsfähigkeit, sowie Ihrer Lebensqualität.

Zweck der klinischen Studie

Trotz guter Ergebnisse in Bezug auf die Lebenserwartung zeigen viele Patienten mit Fontan Kreislauf eine verminderte körperliche Leistungsfähigkeit. Dies ist darauf zurückzuführen, dass (im Vergleich zu einem gesunden Herzen) in einem Fontan Kreislauf die Lungendurchblutung ohne Unterstützung einer Herzkammer stattfindet. Die Muskelpumpe in den Venen sowie die Atemmuskulatur spielen hier eine besonders wichtige Rolle. In diesem Projekt sollen die Auswirkungen eines zu Hause durchführbaren Atemtrainings auf den Allgemeinzustand, die Leistungsfähigkeit und die Lebensqualität untersucht werden. Das Ziel ist, dass in Zukunft alle Patienten nach Fontan Operationen individuell angepasste Trainingspläne erhalten können, mit speziellem Augenmerk auf die Verbesserung der Atemmuskulatur um gute Ergebnisse hinsichtlich Leistungsfähigkeit, Allgemeinzustand und Lebensqualität erzielen zu können.

Ablauf der Studie

Basisuntersuchung: Im Rahmen eines Termins in unserer Ambulanz werden verschiedene Routineuntersuchungen an einem Tag durchgeführt. Diese umfassen ein EKG, eine normale körperliche Untersuchung und eine Echokardiographie. In Folge füllen Sie einen Fragebogen zur Lebensqualität aus und erhalten anschließend eine Belastungsuntersuchung auf dem Fahrrad, einschließlich einer Messung des Sauerstoffgehaltes im Blut mit einer aufgeklebten Sonde am Brustmuskel.

Nach dieser sogenannten Basisuntersuchung werden Sie per Zufall in eine von zwei Gruppen eingeteilt. Befinden Sie sich in der ersten Gruppe, der sogenannten „Trainingsgruppe", beginnen Sie gleich nach Ihrer Basisuntersuchung mit dem Training. Werden Sie der Gruppe 2 zugeteilt, beginnt Ihr Training erst 6 Monate nach der Basisuntersuchung.

Training: Im Anschluss an die Untersuchung wird Ihnen ein Atemtrainingsgerät vorgestellt. Dies stärkt die Atemmuskulatur und wird individuell an Sie angepasst. Ziel ist es die Muskulatur des Brustkorbs sowie das Zwerchfell zu stärken, vor allem für die Einatmung, um eine gute Sauerstoffversorgung zu gewährleisten. Dieses Training wird

von Ihnen zu Hause einmal am Tag für jeweils 10 Minuten durchgeführt. Eine Ansprechpartnerin unserer Klinik steht Ihnen in dieser Zeit dauernd zur Verfügung und wird Sie telefonisch unterstützen. Es wird mit einer Gesamtstudiendauer von eineinhalb Jahren gerechnet. In diesem Zeitraum finden insgesamt 3 Untersuchungen statt sowie am Ende der Studie eine Abschlussuntersuchung.

Risiken und Nebenwirkungen (ggf. auch Nutzen für den Patienten)

Es werden nur etablierte Untersuchungen angewandt, die in unserer Ambulanz bzw. bei einem stationären Aufenthalt regelmäßig stattfinden. Sie können an dieser Studie nicht teilnehmen, wenn Sie in den letzten 3 Monaten eine Medikamentenänderung vorgenommen haben. Ebenfalls sollten Sie in den letzten 6 Monaten keine Herzkatheteruntersuchung erhalten haben und Ihr letzter operativer Eingriff mindestens ein Jahr zurückliegen. Falls Sie in näherer Zukunft einen geplanten operativen Eingriff in Aussicht haben, teilen Sie uns das bitte mit. Teilen Sie uns bitte ebenfalls mit, wenn Sie unter einer Erkältung sowie einer Atemwegsinfektion leiden. In diesem Fall werden Sie ersucht, das vollständige Abklingen der Symptome abzuwarten, bevor Sie das Training fortfahren können. Wir empfehlen ebenfalls, Ihren Atemtrainer nicht mit anderen Personen zu teilen, da Infektionen übertragen werden können. Die Studie gibt keinerlei Therapierichtlinien außerhalb des Trainings vor. Wir hoffen, bzw. rechnen damit, dass sich durch das Atemtraining und die dadurch verbesserte Lungenfunktion auch Ihre Herzkreislaufsituation verbessert. Damit dürfte sich auch Ihre Gesamtleistungsfähigkeit und vielleicht auch Ihre Lebensqualität verbessern. Den Atemtrainer können Sie nach der Studie behalten. Wir hoffen sogar, dass Sie ihn fleißig weiter nutzen.

Vertraulichkeit

Die ärztliche Schweigepflicht bleibt gewahrt. Alle Daten werden ausschließlich pseudonymisiert ausgewertet und veröffentlicht. Die Bestimmungen des Datenschutzes werden eingehalten.

Freiwilligkeit

Die Teilnahme an der Studie ist freiwillig. Sie können Ihre Zusage jederzeit ohne Angabe von Gründen und ohne, dass Sie Nachteile befürchten müssen, zurückziehen.

Vielen Dank, dass Sie an der Studie teilnehmen! Für Rückfragen stehen wir gerne zur Verfügung.

Celina Fritz, M.Sc.
Studienleiterin
Funktionsdiagnostik / Kinderambulanz

PD Dr. med. Nicole Nagdyman
Oberärztin der Klinik
Leiterin der Ambulanz

Prof. Dr. med. Peter Ewert
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und angeborene Herzfehler

Prof. Dr. med. Alfred Hager
Oberarzt der Klinik, Leiter der Ambulanz
Leiter der klinischen Studie

Appendix B

Klinik für Kinderkardiologie und angeborene Herzfehler

Direktor: Prof. Dr. med. P. Ewert

Deutsches Herzzentrum München
des Freistaates Bayern
- Klinik an der Technischen Universität München -

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EINVERSTÄNDNISERKLÄRUNG

zur Studie

Atemtraining bei Patienten mit univentrikulärem Herzen nach palliativer Fontan-Operation

Ich wurde über das Ziel und den Zweck dieser Untersuchung und die praktische Durchführung aufgeklärt. Ich habe die Patienteninformationen erhalten, gelesen und verstanden. Mir wurden alle offenen Fragen beantwortet. Ich hatte ausreichend Zeit, über die Teilnahme nachzudenken. Eine Kopie dieser Einverständniserklärung erhalte ich nach Unterzeichnung.

Ich bin damit einverstanden, dass die im Rahmen der Untersuchung erhobenen Daten aufgezeichnet, wissenschaftlich ausgewertet und archiviert werden. Ich stimme ihrer Veröffentlichung unter der Voraussetzung zu, dass jeder Bezug zur Person unkenntlich gemacht wurde. Ich weiß, dass die Speicherung und Verarbeitung der Daten den Bestimmungen des Datenschutzgesetzes unterliegen. Ich bin damit einverstanden, dass unter Umständen die Aufzeichnungen über die Studie überprüft werden.

Mir ist bekannt, dass ich die Teilnahme an dieser Untersuchung jederzeit ohne Nachteile und ohne Angabe von Gründen mit sofortiger Wirkung zurückziehen kann.

Ich stimme freiwillig der Teilnahme an dieser Studie zu und werde den Pflichten innerhalb der Studie nachkommen.

Patient:

Name des Patienten in Druckbuchstaben	Unterschrift	Datum

Ggf. Inhaber des Sorgerechts:

Name des Sorgerechtinhabers in Druckbuchstaben	Unterschrift	Datum

Name des Sorgerechtinhabers in Druckbuchstaben	Unterschrift	Datum

Grundsätzlich sind die Unterschriften beider Sorgerechtinhaber notwendig. Liegt nur die Unterschrift eines Sorgerechtinhabers vor, versichert dieser gleichzeitig, dass dieser im Einverständnis des anderen handelt oder das alleinige Sorgerecht hat.

Appendix C

Anleitung für zu Hause

Deutsches Herzzentrum München
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Klinik an der Technischen Universität München

Atemtechniken

Es gibt drei verschiedene ruhige Atmungsformen: Brustatmung, Bauchatmung und Flankenatmung.

Brustatmung

Die Einatmung mit der Brustatmung erfolgt durch das Zusammenziehen der Zwischenrippenmuskeln, das Zwerchfell ist unbeteiligt. Nur das obere und mittlere Drittel der Lungen wird bei dieser Atmungsform belüftet. Diese Atemtechnik wird nicht gezielt beim Atemtraining mit dem POWERbreathe angewendet.

Bauchatmung

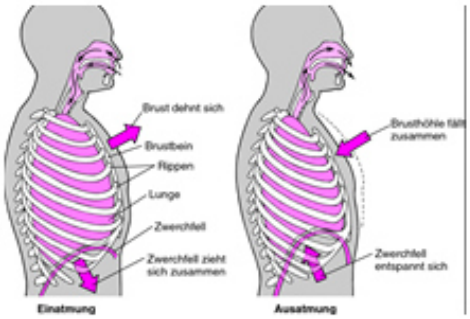
Die Einatmung mit dieser Atemtechnik erfolgt ausschließlich durch die Anspannung des Zwerchfells. Während des Einatmens senkt sich das Zwerchfell und die Lungen dehnen sich infolge der Vergrößerung des Brustkorbs passiv aus. Durch den Unterdruck wird Luft über die Atemwege in die Lunge eingesogen. Ersichtlich ist dies in der Außenwölbung der Bauchwand, da sie aufgrund des Platzmangels durch die Bauchorgane nach außen gedrückt wird.

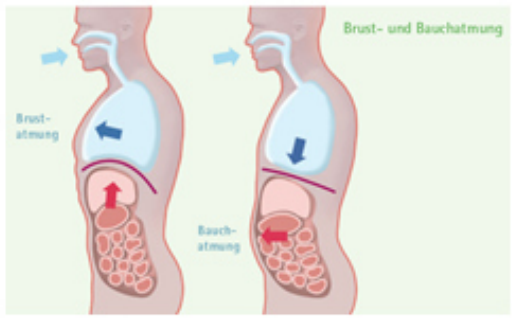
Die Ausatmung erfolgt durch das aktive Zusammenziehen der Bauchmuskeln. Das Zwerchfell ist entspannt. Die Bauchdecke flacht ab und das Lungenvolumen verkleinert sich. Die Luft strömt über die Atemwege nach außen.

Flankenatmung

Die Flankenatmung ist eine Mischform aus Bauch- und Brustatmung. Die Einatmung erfolgt über eine aktive Anspannung des Zwerchfells und der äußeren Zwischenrippenmuskeln. Es folgt eine passive Dehnung der Lunge, durch den Unterdruck wird Luft über die Atemwege in die Lunge eingesogen. Ersichtlich ist dies mit einer seitlichen Vergrößerung des Thorax. Mit dieser Atemtechnik wird die ganze Lunge belüftet.

Während der Ausatmung entspannen sich die Zwerchfell- und die Zwischenrippenmuskulatur. Die Lungen verringern infolge ihrer Elastizität und der Verkleinerung des Brustkorbs ihr Volumen. Die Luft strömt über die Atemwege nach außen.





Ablauf des Trainings

1. Aufwärmen

Das Aufwärmen erfolgt ohne POWERbreathe (bei Trainingsstufe 1), wenn...

- noch nicht 2 Wochen lang mit dem POWERbreathe trainiert worden ist
- die Atemtechniken noch nicht automatisiert sind
- der Trainingswiderstand auf Stufe 1 eingestellt ist

Bauchatmung: Hände flach auf den Bauchnabel legen, beim Einatmen durch den Bauch die Hände nach vorne drücken. Insgesamt fünfmal tief einatmen. Diese Übung kann im Stehen, Sitzen (in aufrechter Position) oder Liegen erfolgen.

Flankenatmung: Hände seitlich auf die Rippen legen, beim Einatmen mit den Rippen die Hände zur Seite drücken. Insgesamt fünfmal tief einatmen. Diese Übung kann im Stehen, Sitzen (in aufrechter Position) oder Liegen erfolgen.

➔ Die Reihenfolge der Atemtechniken kann frei gewählt werden. Eine sich abwechselnde Reihenfolge ist selbstverständlich auch möglich.

Das Aufwärmen erfolgt mit POWERbreathe (ab Trainingsstufe 2), wenn...

- bereits 2 Wochen lang mit dem POWERbreathe trainiert worden ist
- die Atemtechniken automatisiert sind
- der Trainingswiderstand mindestens auf Stufe 2 eingestellt ist

Bauch- und Flankenatmung: Den Widerstand verglichen mit der Trainingsintensität um eine Stufe verringern. Eine aufrechte Position im Sitzen oder stehen einnehmen und zum Aufwärmen 20 Trainingsatemzüge durchführen.

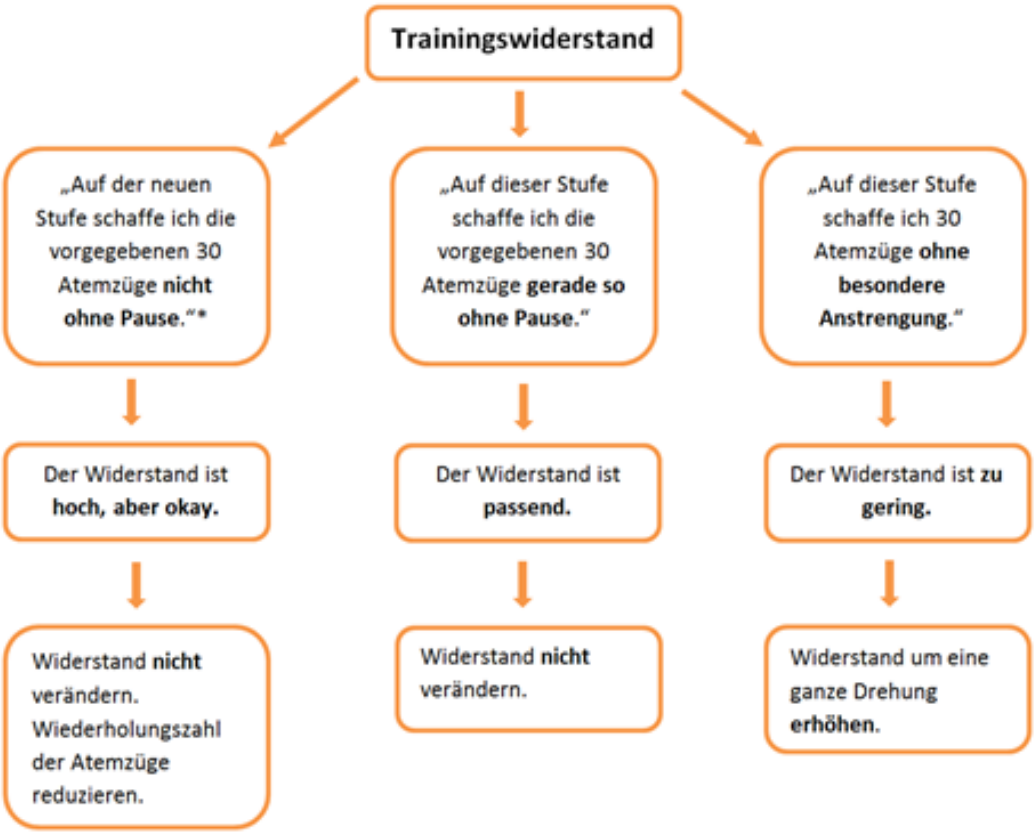
2. Training

Den Trainingswiderstand einstellen und eine aufrechte Position im Sitzen oder Stehen einnehmen. Ziel ist, auf der aktuellen Stufe dreimal je 30 Trainingsatemzüge durchzuführen. Die Länge der Pausenzeit ist vom aktuellen Befinden abhängig und wird nicht vorgegeben. Zur Einstellung des passenden Trainingswiderstands s. nächste Seite.

Zu beachten:

- bei Erhöhung des Widerstands an die passende Wiederholungszahl herantasten
- keinen Muskelkater provozieren
- in Durchgang 2 und 3 die Anzahl der Atemzüge nicht in der aktuellen Trainingseinheit steigern

3. Einstellen des Trainingswiderstands



* Die vorgegebenen 30 Atemzüge nicht erzwingen. In Durchgang 2 und 3 lediglich die Anzahl, der in Durchgang 1 geschafften Atemzüge, wiederholen. Keinen Muskelkater provozieren.

Kontraindikationen

- Schmerzen: Training sofort abbrechen und Arzt aufsuchen
- unangenehmes Gefühl im Ohr: Training abbrechen, evtl. Arzt aufsuchen
- Erkältung, Atemwegsinfektionen: warten, bis Symptome vollständig abgeklungen sind