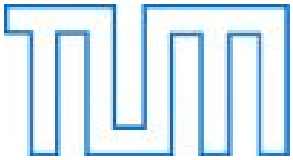

Technische Universität München

Lehrstuhl für Präventive Pädiatrie
Fakultät für Sport- und Gesundheitswissenschaften
Klinik für angeborene Herzfehler und Kinderkardiologie
Deutsches Herzzentrum München

Functional outcomes in young patients with complex congenital heart disease

Julia Theresa Hock

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Vorsitzende(r):

Prof. Dr. Jürgen Beckmann

Prüfer der Dissertation:

1. Prof. Dr. Renate Oberhoffer-Fritz
2. Prof. Dr. Dirk Haller

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SUMMARY

Young patients with congenital heart defect (CHD) are increasing in number because of improvements in surgical and medical management. Their increasing prevalence makes them an important target for research. Research regarding improving their quality of daily life has become very important. Functional outcomes reflected in motor development, exercise capacity, and lung volumes are important parameters to assess the clinical status of these young patients.

The first two studies aimed to demonstrate the post-operative state of functional outcomes (exercise capacity, health-related physical fitness (HRPF), health-related quality of life and arterial stiffness) in patients with total cavopulmonary connection (TCPC), the most complex CHD after palliation, and tetralogy of Fallot (rToF), the most common cyanotic CHD, compared to a healthy reference cohort.

Both studies show that the patients are impaired in exercise capacity and HRPF. The studies demonstrate the importance of early examination of exercise capacity and HRPF to treat patients if needed.

The third study was performed to see if exercise capacity (peak $\dot{V}O_2$) could be improved in young patients with rToF utilizing a six-month inspiratory volume-oriented breathing training without an aerobic exercise component at home. The analyses showed that breathing training increased both exercise capacity and lung volumes. A positive correlation between training frequency and increase in peak $\dot{V}O_2$ was seen.

All studies underscore the importance of early screening and treatment of young patients with complex CHD to improve their functional status and thus their quality of life.

ZUSAMMENFASSUNG

Das Patientenkollektiv der Kinder, Jugendlichen und jungen Erwachsenen mit angeborenem Herzfehler (AHF) rückt immer mehr in den Fokus der Forschung. Aufgrund der enormen Fortschritte der letzten Jahrzehnte in der Medizin, wird auch das alltägliche Leben der jungen Patienten immer wichtiger. Insbesondere funktionelle Ergebnisse wie die motorische Entwicklung, die Belastungskapazität oder das Lungenvolumen sind wichtige Parameter zur Beurteilung der aktuellen Situation dieser Patienten.

Ziel der ersten beiden Studien war es, den aktuellen Stand der funktionellen Ergebnisse (Leistungsfähigkeit, gesundheitsbezogene körperliche Fitness (HRPF), gesundheitsbezogene Lebensqualität und arterielle Steifigkeit) bei Patienten mit totaler cavopulmonaler Konnektion (TCPC), der komplexeste AHF nach palliativer Operation und der Fallot'schen Tetralogie nach chirurgischer Korrektur (rToF), der häufigste zyanotische Herzfehler, im Vergleich zu einer gesunden Referenzkohorte aufzuzeigen. Beide Studien zeigen, dass die körperliche Belastbarkeit und gesundheitsbezogene körperlichen Fitness (HRPF) der Probanden eingeschränkt ist. Die Ergebnisse unterstreichen, wie wichtig eine frühzeitige Untersuchung der körperlichen Belastbarkeit und der HRPF ist, um Patienten bei Bedarf behandeln zu können.

Die dritte Studie zielte auf die Verbesserung der körperlichen Leistungsfähigkeit bei jungen Patienten mit rToF durch ein sechsmonatiges inspiratorisches volumenorientiertes Atemtraining ab. Die Analysen zeigten, dass das Atemtraining sowohl die maximale Leistungsfähigkeit als auch das Lungenvolumen verbesserte. Es zeigte sich eine positive Korrelation zwischen der Trainingshäufigkeit und dem Anstieg der Belastbarkeit.

In allen Studien wird die Bedeutung einer frühzeitigen Untersuchung und möglicher Behandlung funktioneller Ergebnisse bei jungen Patienten mit komplexem AHF unterstrichen, um sie vor möglichen Folgen im späteren Leben zu bewahren.

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LIST OF ABBREVIATIONS

AGD	Analysis of Growth Data
ATS	American Thoracic Society
bpm	beats per minute
CHD	congenital heart disease
CPET	cardiopulmonary exercise test
cm	centimeter
CO_2	carbon dioxide
cBP	central blood pressure
DORV	double outlet right ventricle
ECG	electrocardiogram
e.g.	Latin: exempli gratia (*for example*)
GLI	Global Lung Initiative
FEV1	forced expiratory volume within the first second
FVC	forced vital capacity
HC	healthy control
HRPF	health-related physical fitness
HRQoL	health-related quality of life
KINDL-R	questionnaire for children, which asks about their quality of life
kg	kilogram
km/h	kilometers per hour
IBM	International Business Machines
ID	identity document
I.E.M.	Industrial Electric Mfg.
L	liter
LMS	Least-Mean-Squares Algorithm
ml	milliliter
min	minute
n	number of patients
p	p-value (statistical variable)
peak$\dot{V}O_2$	peak oxygen uptake [ml/min/kg]
PWV	pulse wave velocity
QoL	quality of life

RC	reference cohort
RVOTO	right ventricular outflow tract obstruction
SD	standard deviation
SPSS	Statistical Package for the Social Sciences
TCPC	total cavopulmonary connection
rToF	tetralogy of Fallot after repair
ToF+PA	pulmonary atresia of Fallot-Type
USA	United States of America
$\dot{V}_E/\dot{V}CO_2$	needed liters to exhale one liter of carbon dioxide
$\dot{V}O_2$	oxygen uptake

LIST OF FIGURES

1 INTRODUCTION

Worldwide the incidence of congenital heart disease (CHD) is 9.3 per 1,000 newborns.[1] In Germany 10.7 per 1,000 live births are born with a CHD.[2] A heart defect is one of the most common congenital malformations. Particularly in infancy, the mortality rate has fallen sharply, and today is similar to that of the healthy population between the ages of 18 and 64.[3,4] This increased life expectancy in today's children and young people with CHD entails new tasks and challenges for science, prevention, treatment, and aftercare.

One aim of medical science today is to optimize patients' daily performance and increasing their quality of life (QoL). QoL is dependent on many factors including integration into everyday life, school, education, and eventually work, but also functional outcomes impact patients' QoL.

Due to medical progress, mostly newborns or infants undergo a surgical repair or at least a palliative correction, which guarantees survival.[5] Lifelong care and, if needed, treatment of these patients is essential and requires the investigation of many different aspects.[6] Though growing-up is fairly normal, restrictions in functional outcomes often occur.[7]

2 STUDY PURPOSES

This thesis evaluates functional outcomes in contemporary children and young patients with two complex congenital heart defects. Furthermore, it investigates whether an inspiratory volume-oriented breathing training in young patients who underwent surgical repair after tetralogy of Fallot increases their exercise capacity.

AIM OF STUDY 1

The first paper deals with contemporary children with total cavopulmonary connection (palliative surgery due to univentricular heart defect) and examines their exercise capacity, health-related physical fitness, and health-related quality of life. Data were evaluated retrospectively, and results were compared to healthy peers.

AIM OF STUDY 2

The second paper handles current children with tetralogy of Fallot after surgical repair and investigated their exercise capacity, health-related physical fitness, and arterial stiffness. Data were analyzed retrospectively, and results were compared with a healthy reference cohort.

AIM OF STUDY 3

The third study was a prospective randomized controlled intervention trial in children and young adults with repaired tetralogy of Fallot, conducted to increase their functional outcomes (exercise capacity, spirometry, and breathing excursion) with daily inspiratory volume-oriented breathing training.

3 MEDICAL BACKGROUND

3.1 NORMAL HEART FUNCTION

A normal heart (Figure 1) consists of four chambers, four valves, and both, small and large vessels that maintain blood flow to the entire body.[8]

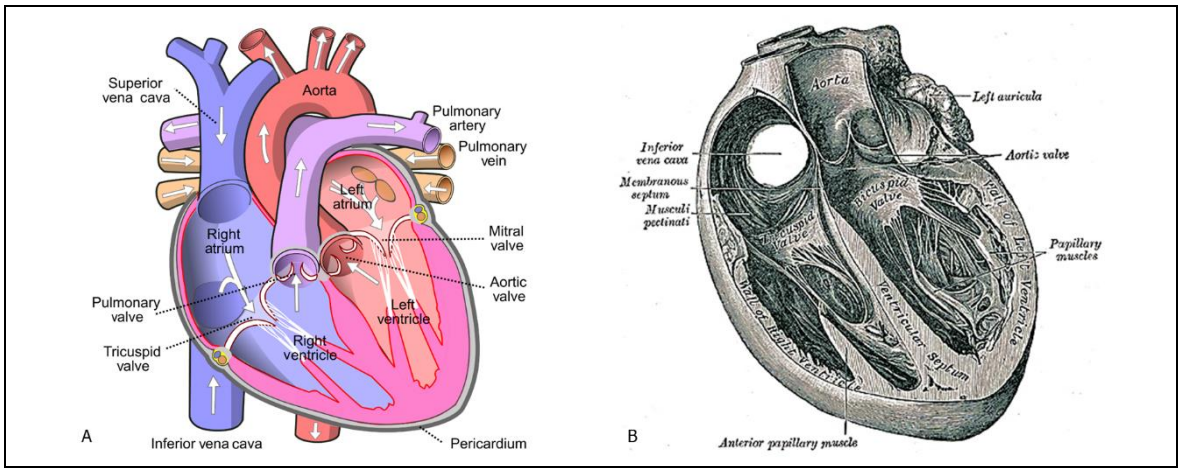

Figure 1: Anatomy of a normal heart

A:[9] schematic with four valves and large arteries
B:[10] with the heart chamber wall and papillary muscles

The right heart is responsible for the pulmonary circulation (low-pressure), and the left heart for the systemic circulation (high-pressure). Accordingly, the left ventricle is muscularly better equipped than the right one (Figure 1 B: chamber walls and papillary muscles in the left ventricle are better developed to generate the higher pressure).[8]

Abnormalities, such as slight changes or defects in anatomy can have a major impact on the hearts' functional capacity and longevity and therefore on the patient himself.

3.2 COMPLEX CONGENITAL HEART DISEASES

Since 1930, the prevalence of congenital heart disease (CHD) increased from less than one to approximately nine per 1,000 live births (Figure 2).[1]

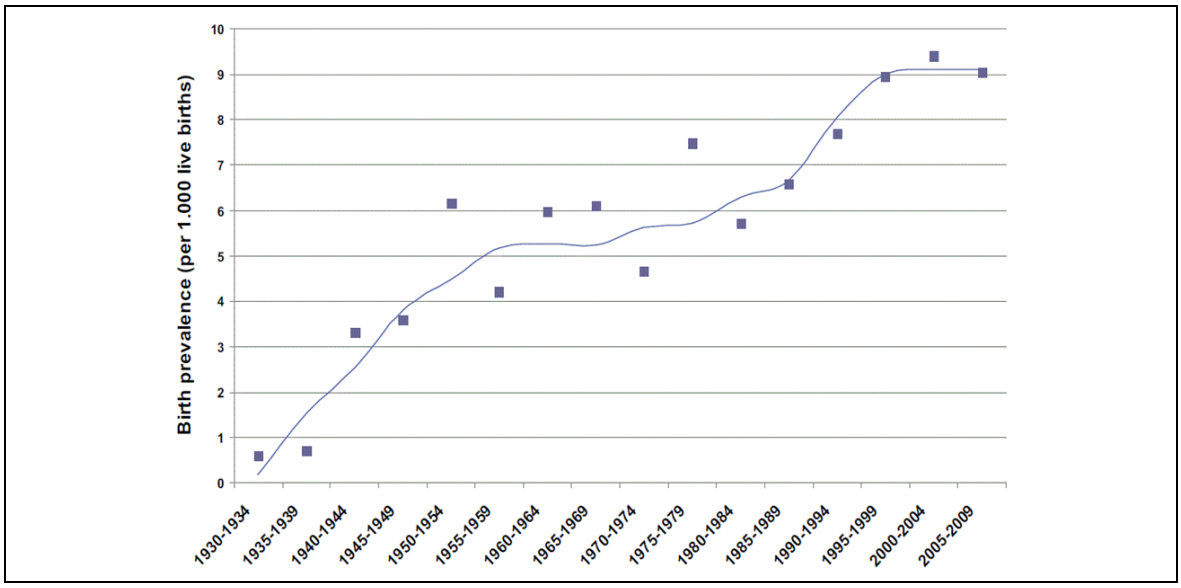

Figure 2: Total CHD Birth Prevalence Over Time [in five years intervals]

The illustration was taken from van der Linde and collegues[1]; CHD: congenital heart disease

Lindinger et al.[2] published in 2010 that 10.7 of 1,000 live births suffered from a CHD. Their classification extends from mild (6.5/1,000 alive newborns, including atrial septal defect and patent foramen ovale), moderate (3.0/1,000 alive newborns, including aortic stenosis and coarctation of the aorta) to complex (1.3/1,000 alive newborns, including tetralogy of Fallot, transposition of the great arteries and single-ventricle).[2]

These 1.3/1,000 newborns with a complex CHD represent 12.0% of all infant CHD patients.[2] Most patients with complex CHD are cyanotic due to a common pulmonary and systemic circulation (Figure 3 and Figure 4). Palliative or corrective surgery is usually required for survival. The long-term outcome and survival in this patient group have increased significantly.[11] Children are more likely to reach adulthood.[12-14] These patients with complex CHD remain in need of regular evaluations and eventual treatment during their lifetime.[6] This includes basic examination procedures such as a regular electrocardiogram (ECG), echocardiography to evaluate the valves and heart muscle function, a 24-hour ECG to evaluate arrhythmia, as well as performance evaluation using cardiopulmonary exercise tests.

UNIVENTRICULAR HEART

Out of 1,000 of all alive newborn children in Germany, 0.3 have a single-ventricle morphology.[2] Anatomically, a single ventricle does not mean that only one ventricle is present, but rather that only one functions properly.[15] Thus, either the tricuspid or the mitral valve is not sufficiently developed, which means underdevelopment of the left (mitral valve atresia or hypoplasia) or right (tricuspid valve atresia or hypoplasia) ventricle. However, other single ventricle morphologies are much more complex (e.g. double inlet left ventricle). Usually, these CHD needs to be diagnosed prenatally, to ensure the best possible prospects.[15,16]

The most common single lesion is the hypoplastic left heart syndrome (HLHS, Figure 3 A), which was diagnosed in half of the patients with a single ventricle in Lindinger et al.[2], representing 1.4% of all CHD.

The first successful surgical palliation of tricuspid atresia was reported in 1971.[17] If a surgical biventricular repair (as in e.g. pulmonary atresia with ventricular septal defect) is not possible, young patients nowadays need to undergo three-step palliation to make survival possible.[18,19] Patients who undergo the last of the three steps, the total cavopulmonary connection (TCPC, Figure 3 B), have good event-free survival.[20] The last surgery (TCPC) aims to drain all the blood from the body's circulation directly into the lungs since no functioning chamber can be interposed. This is done by connecting the inferior vena cava with the right pulmonary artery. This can be an intra- or extracardiac conduit (Figure 3 B).

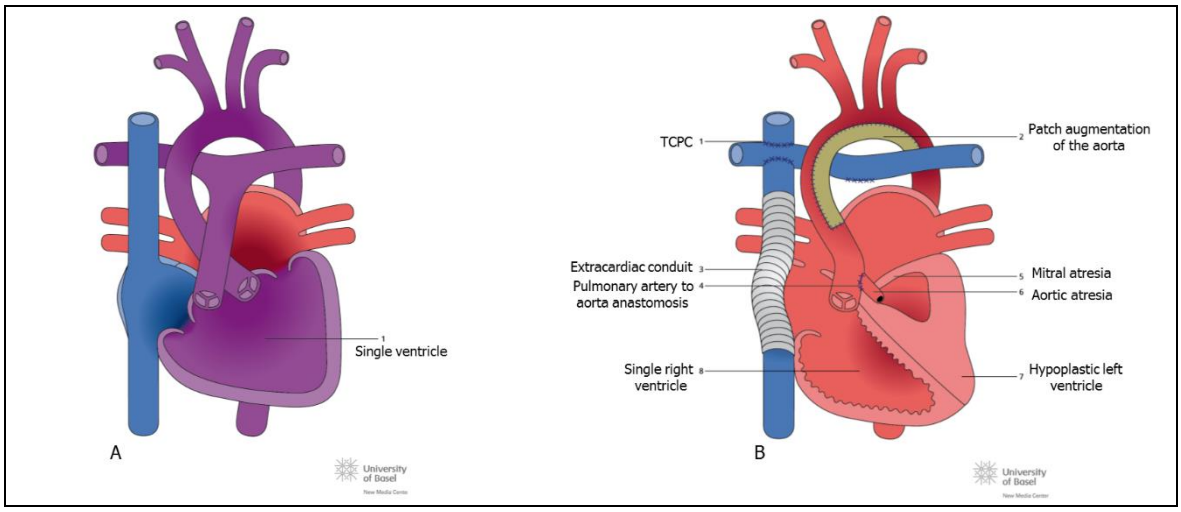

Figure 3: Schematic single ventricle and HLHS after TCPC palliation

A: "Single ventricle"
B: "TCPC with extracardiac conduit for HLHS"
HLHS: hypoplastic left ventricle, TCPC: total cavopulmonary connection

The blood coming directly from the body (blue in the heart diagram, Figure 3 B) is thus enriched with oxygen from the lungs. It is pumped via the right atrium and the right ventricle into the systemic circulation (red in the heart diagram, Figure 3 B). A so-called "overflow" valve is often created in the area of the extracardiac tunnel. This forms a connection between the tunnel and the right atrium and ensures that blood can drain into the right atrium if there is high blood pressure in the pulmonary circulation. This makes it easier for the pulmonary circulation to adapt to the new blood flow conditions. The overflow valve usually closes spontaneously once circulatory conditions have stabilized. If this does not happen, it can be closed using a cardiac catheter. After surgical palliation, patients have two separate circulations with serial blood flow. The pulmonary circulation is a passive one (no heart muscle between caval veins and pulmonary artery) and the systemic circulation is driven by the single ventricle.[19,15,21]

Depending on which (left or right morphology) ventricle is leading, patients may suffer from different long-term effects.[15] Two recently published studies from Ono et al.[20,22] analyzed the long-term outcome of patients who underwent a TCPC. According to this, the current patients, compared to those who underwent a classic Fontan-procedure do have much fewer complications in the follow-up. Still, arrhythmia (9%) and abnormal ejection fraction (11.8%) are present.[20] Close supervision is advisable and strongly recommended.[23,6]

TETRALOGY OF FALLOT

Every year, 0.3 per 1,000 alive infants born in Germany have tetralogy of Fallot (ToF).[2] A ToF (Figure 4 A) is the most common cyanotic CHD.[2,1] Its symptoms differ from almost none to very complex and serious.[24]

Patients born with ToF have a displacement of the infundibulum septum to the right, anterocephal. This results in (I) a right-ventricular outflow-tract obstruction (RVOTO), (II) a subaortic ventricular septal defect, (III) an overriding aorta which competes for flow with the pulmonary artery, and (IV) right ventricular hypertrophy due to exposure to systemic pressure.[25]

Patients may have a right-to-left shunt and therefore they suffer from mixed oxygenated (red) and deoxygenated (blue) blood (Figure 4 A).[26]

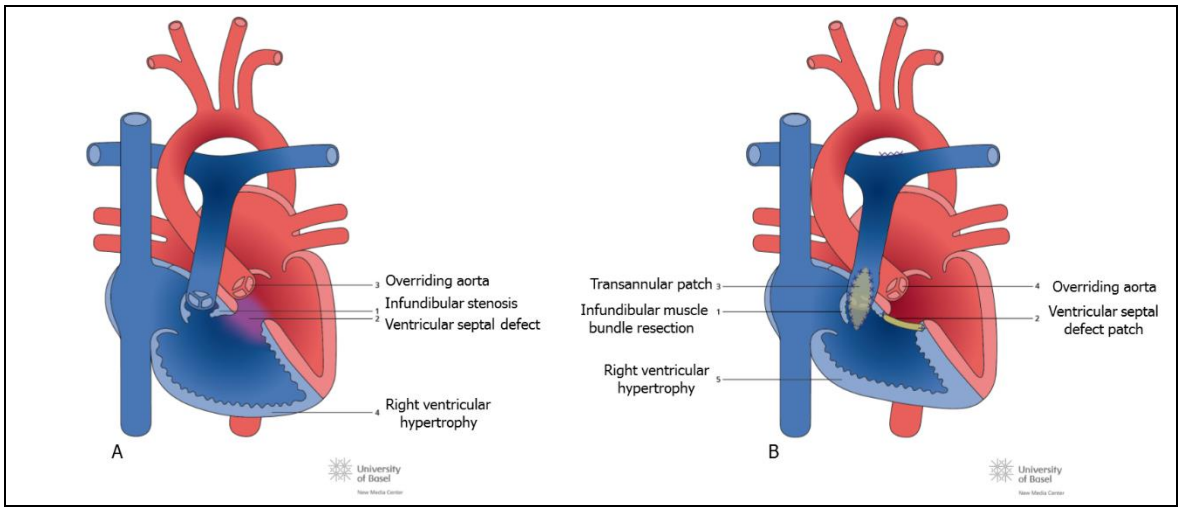

Figure 4: Tetralogy of Fallot before and after surgical repair

A: "Tetralogy of Fallot (TOF)"
B: "Tetralogy of fallot [sic!] repair with transanular [sic!] patch"

Modified (legend added) illustrations were taken from http://www.chd-diagrams.com and licensed under Creative Commons Attribution-Non-Commercial-No-Derivatives 4.0 International License by the New Media Center of the University of Basel.

The infants may be born without cyanosis (if the RVOTO is small, sometimes unknown at birth) or cyanotic (oxygen saturation <90%), which causes a bluish color to the skin. The danger of the latter group of newborns is, that during a hypoxemic attack the pulmonary stenosis may affect their blood flow and therefore they may lose consciousness.[27]

Normally, if the CHD is diagnosed prenatal, patients typically undergo corrective surgery (one example in Figure 4 B) within the first year.[27] During surgery, patients' septal defect is closed, the aorta "replaced", the pulmonary artery extended, or in some cases, the pulmonary valve is replaced.[25]

In the long-term course after the repair, in particular, the right-ventricular function and pulmonary artery condition are of high interest may be affected by the surgery. Late complications can include pulmonary valve regurgitation (which may require valve replacement), new-onset RVOTO, pulmonary stenosis, but also arrhythmias such as ventricular arrhythmia, which is still the most often cause of death in these patients.[26,25] Life-long close follow-up is required and strongly recommended.[23,6,27]

3.3 FUNCTIONAL OUTCOMES

EXERCISE CAPACITY

Exercise capacity can be expressed as peak oxygen uptake (peak $\dot{V}O_2$ in ml/min/kg). It reaches from 3.5 ml/min/kg[28] at rest up to over 70 ml/min/kg in high-class elite male runners.[29] Reference values (percentage of predicted) depend upon age, sex, and height.[30-32] Peak $\dot{V}O_2$ represents the highest oxygen consumption from the air which flows thru the lungs for transporting oxygen thru the cardiovascular system[33] during a maximal effort test over a 30-second period.[34,35] Mostly, this maximal effort test is a cardiopulmonary exercise testing (CPET). By using an airtight mask (Figure 5) which is connected to a test-specific machine, a breath-by-breath measurement records the patients' oxygen consumption.[36]

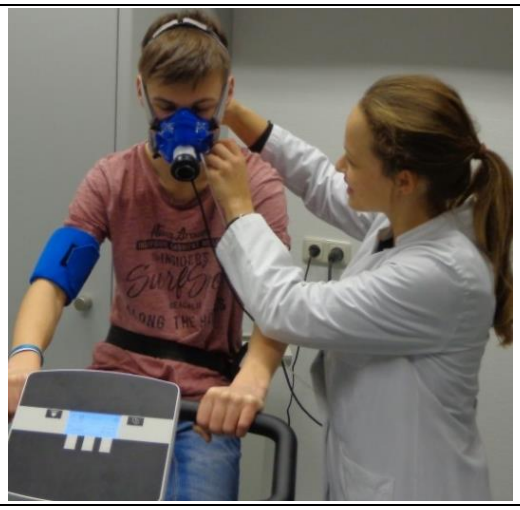

Figure 5: Patient being prepared for the examination (CPET) at the *Deutsches Herzzentrum München*

CPET: cardiopulmonary exercise test

A CPET is an objective examination that provides valid monitoring and data in both the respiratory and cardiovascular areas simultaneously.[37] It is well-established to evaluate particularly chronically ill patients[38,39] but also professional athletes[40,41] and to assess their current health status as well as prognosis e.g. for patients with heart failure.[42]

Further relevant measurement during CPET is the patients' ventilatory efficiency. It expresses the relationship of ventilated liters of air which are required to exhale one liter of carbon dioxide (CO_2).[40,31] It is presented as a slope and expressed as $\dot{V}_E/\dot{V}CO_2$slope. As a reference, a good result is less than 34 liter, which can be further subdivided (< 30 L: normal, 30-33.9 L: lightly increased, ≥ 34 L increased).[43,44]

More parameters are for example anaerobic threshold, respiratory exchange ratio, or oxygen pulse.[34] It is required to control patients' ECG during a maximal effort test to not overlook any rhythm disturbances or ischemia.[34]

HEALTH-RELATED PHYSICAL FITNESS

The development of motor skills is closely related to daily exercise in childhood and adolescence, which positively affects children's physical fitness and can prevent them from physical or possible mental disorders.[45-48] Measurement of health-related physical fitness[49] (HRPF) assesses muscular strengths, endurance, and flexibility. All components give important impressions on patients' motor development: if for example, a child is not adequately able to perform a curl-up, further investigations may help to prevent it from later-onset impairments.[50] To be noted is, that HRPF differs in male and female children and adolescents. For example, the development of strength in boys increases significantly at an age of 13 and older, whereas with girls a small increase is to be registered.[50] Children and adolescents can increase their HRPF if they do sports or at least train their skills.[51,52,50] Comparison data need to be taken from peers of a similar birth cohort due to its change during the last decades.[51]

HEALTH-RELATED QUALITY OF LIFE

Health-related quality of life (HrQoL) is an important concept which expresses individuals' physical and psychological well-being.[53,54] It can be measured self-reported or proxy-reported to assess the patients' temporary situation.[55-57] Not only with healthy children a survey of HrQoL can give information about their physical and mental condition but also with chronically ill children this can help clinicians and therapists with treatments.[58,59] Commonly, questionnaires are used to assess HrQoL in children and adolescents. Current reference data from peers are needed to compare samples adequately.[57]

ARTERIAL STIFFNESS

The vascular function can be described by determining arterial stiffness. The systolic blood pressure in the aorta affects the afterload on the heart. The total peripheral resistance influences this. For example, increased stiffness of the aorta leads to an increased characteristic impedance of the aorta. This initially leads to an increased systolic peripheral blood pressure, which in turn results in, among other things, left-sided hypertrophy. This results in increased expulsion time and diastolic dysfunction. In the long term, it leads to heart

failure. All these relationships prove the relevance for the practice of measuring vascular stiffness and, if necessary, treating certain parameters to prevent end-organ damage.[60-62] Independent variables are e.g. the pulse wave velocity (PWV) or central blood pressure (cBP).[60,61,63,64]

PWV reflects the speed with which the blood passes the body[65]. It is mainly influenced by blood pressure, age, and, to a small extent, by cardiovascular risk factors[66] and therefore can provide information about possible end-organ damage due to (too) high blood pressure[67,68]

Central systolic blood pressure (cBP) is directly effective at the heart and the central nervous system[66,69] and can be measured directly at the aorta. Today calculations are used, which are based on the measurement of the pulse wave analysis.[69] The measurement can be seen as a good to very good possibility to obtain an effective therapy monitoring, especially in hypertension patients.[70]

It is conceivable that increased arterial stiffness at a young age can lead to an increased cardiovascular risk already in youth and young adulthood.[71]

Only since 2015, percentiles for children and young people between the ages of eight and 21 exist and allow comparisons between them and measurements in other cohorts.[68]

3.4 VOLUME-ORIENTED INSPIRATORY BREATHING TRAINING

Train the lung is a well-established method in training and rehabilitation in both, sick[72-74] and healthy[75] people. It is conceivable that by improving the respiratory pump, the venous return flow can be increased.[76] Improved ventilation of the lungs reduces resistance in the pulmonary circulation, which in turn relieves the heart indirectly[77] which may lead to an increase in patients' exercise capacity.[78,79]

SPIROMETRY

Spirometry tests someone's lung volumes including forced vital capacity (FVC), forced expiratory volume within the first second (FEV1), and its ratio.[80] FVC is defined as the volume, which can be maximally exhaled after maximum inhalation and it measures the lungs' and chest's elasticity, including the respiratory muscles' strengths.[81] FEV1 is the first second at which full pressure is exhaled.[81]

Spirometry can provide initial indications of possible restrictions (FVC z-score < 1.645) or obstructions (FEV1/FVC z-score < 1.645) in lung function. If this is the case, body plethysmography, as well as a measurement of the diffusion capacity, is recommended.[82] Furthermore, the FEV1 is to calculate a patient's breathing reserve within a CPET[83,84] and should therefore be measured routinely before a CPET.

BREATHING EXCURSION

The breathing excursion is a valid test to determine patients' thoracic flexibility for expansion with air.[85,86]

4 METHODOLOGY

In study one and study two, exercise capacity and HRPF were measured using the same instruments. In TCPC patients, additionally, HRQoL was measured with the KINDL-R questionnaire[54] and in rToF patients, central blood pressure was measured using an oscillometric device.[87,88]

Both studies followed the Declaration of Helsinki and were registered at "Deutsches Register für Klinische Studien" as "FOOTLOOSE" (ID: DRKS00018853) and approved by the local ethical board of the Technical University of Munich (project number: 314/14). Written consent was obtained from all participants and their guardians. The project includes all kinds of CHD patients.

In study three, the possible effect of volume-oriented inspiratory breathing training on exercise capacity, lung function, and breathing excursion was evaluated. The study followed the Declaration of Helsinki and was approved by the local ethical board of the Technical University of Munich (project number: 4/17S). Written consent was obtained from all participants and their guardians and the study was registered as a randomized non-blinded clinical trial at the "Deutsches Register für Klinische Studien" (ID: DRKS00011363). The primary outcome was the improvement of exercise capacity (peak $\dot{V}O_2$); secondary outcomes included changes in lung volumes and thoracic flexibility.

All three studies investigate only patients who underwent surgical repair (rToF) or palliation (TCPC). Some patients participated in study two (functional outcomes in rToF patients) and three (intervention study in rToF).

4.1 PATIENTS SELECTION

STUDY 1 AND 2

For these two cross-sectional studies, patients were eligible for inclusion if seen at routine follow up appointment at the outpatient department in the Clinic for Congenital Heart Defects and Pediatric Cardiology of the *Deutsches Herzzentrum München*. They had to be between six and 17 years of age and accompanied by a guardian.

STUDY 3

The study population for the prospective randomized intervention study consisted of patients with repaired tetralogy of Fallot (rToF) including double-outlet right ventricle of Fallot-type and pulmonary atresia with a ventricular septal defect and age of eight to 25 years. The inclusion of patients was performed first until the age of 17 and then from young (18 years of age) to old (last inclusion 23 years of age, amendment proved at the local ethical board of the Technical University of Munich). All patients were contacted in advance due to the interventional study design. If interested, the necessary information was sent. Patients and their legal guardians had more than one day to overthink their participation before an appointment for the examination was made and the written consent form signed. The exclusion criteria consisted of bronchial obstruction (FEV1/FVC: standard deviation < 1.645), change in medication within the last 3 months, catheterization within the last 6 months, heart-surgery within the last 12 months, planned surgery within the next 36 months, severe left heart failure (New York Heart Association class IV), frequent arrhythmia, pacemaker and/or acutely infected lungs.

4.2 FUNCTIONAL OUTCOMES

EXERCISE CAPACITY

Most patients in all studies performed a symptom-limited cardiopulmonary exercise test (CPET) following the American College of Cardiology and American Heart Association guidelines (latest update 2002).[89,90]

All tests were done on a bicycle or a treadmill (if needed only). After 3-minutes of rest, patients started pedaling or walking without any load. This was followed by a ramp protocol, with an increase of 5, 10, 15, 20, 30, or 40 watts/minute or 1.0km/h per minute, depending on the expected watt or speed to determine 8-12 minutes for the most appropriate test. After achieving the individual metabolic exhaustion (respiratory quotient >1.05 or 1.10 in adults,[91] respectively), monitoring for 5 minutes followed (due to possible arrhythmia or circulation problems, etc.), whereas the patients pedaled or walked 2-3 minutes without any load. The recording was breath-by-breath following current literature.[36] Peak $\dot{V}O_2$ was set manually (at the end of the resistance test) using the 9-field Wasserman graph in Field 1 (Figure 6) as the mean of a 30 seconds measure-interval.[31]

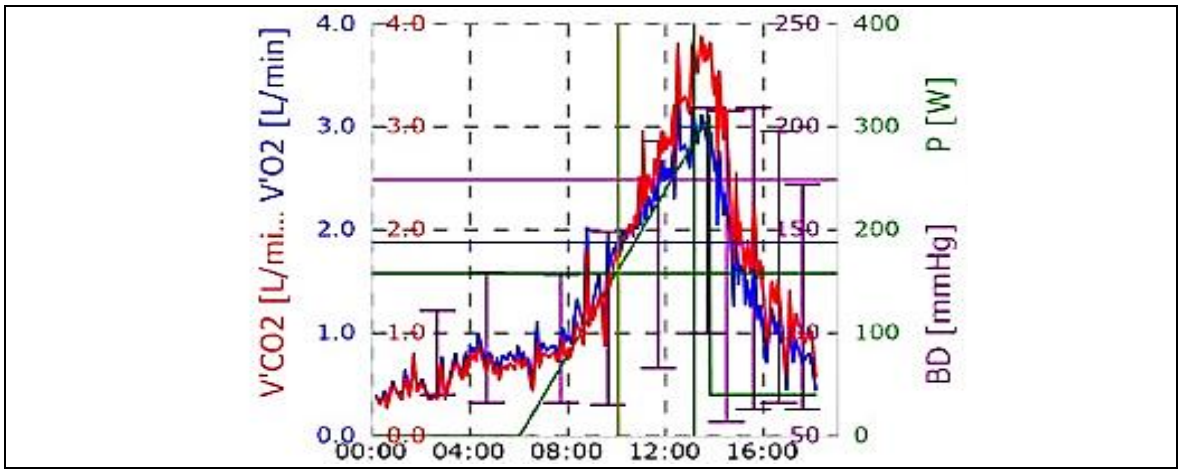

Figure 6: Field 1 in 9-field Wasserman graph, used for determining peak $\dot{V}O_2$

V'CO [L/min]: carbonate discharge in liter per minute, V'O2 [L/min]: oxygen uptake in liter per minute, BD [mmHg]: "Blutdruck"=blood pressure in millimeter of mercury, P [W]: power=resistance in watt

As reference data for children until the age of seventeen[30] were used:

< 12 years of age in male and female:

$$\text{peak } \dot{V}O2 = \frac{(37.1 * height\ (cm) - 3770.6)}{weight\ (kg)}$$

12 – 17 years of age in male:

$$\text{peak } \dot{V}O2 = \frac{(43.6 * height\ (cm) - 4547.1)}{weight\ (kg)}$$

12 – 17 years of age in female:

$$\text{peak } \dot{V}O2 = \frac{(22.5 * height\ (cm) - 1837.8)}{weight\ (kg)}$$

For patients from 18 to 25 years of age, extrapolated adolescent norm values from these formulas were used.

The estimated ventilatory efficiency ($\dot{V}E/\dot{V}CO_2$ slope) indicated, how many liters of air patients must exhale to eliminate one liter of CO_2. The slope was limited to the linear part of the curve, excluding values beyond the respiratory compensation point (Figure 7).

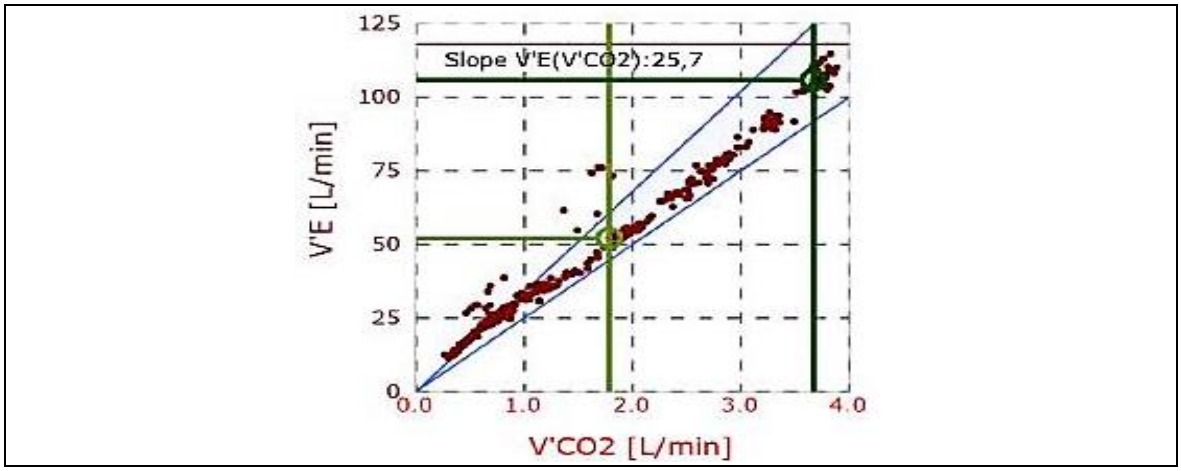

Figure 7: Field 6 in 9-field Wasserman graph, used for determining $\dot{V}E/\dot{V}CO_2$ slope

V'E [L/min]: ventilation in liter per minute, V'CO2 [L/min]: carbonate elimination in liter per minute

HEALTH-RELATED PHYSICAL FITNESS

Both strength and mobility were tested (Figure 8).

The mobility of the shoulder joints and muscles (shoulder stretch, Figure 8 A) was measured for each side separately. One hand was stretched upwards, the other downwards and brought together as close as possible behind the back. The distance between the index fingers was measured with the hands closed (fist). A negative result showed a positive and existing distance between the fists. The best possible result in this test was "zero" if the fists touched each other. For the statistical evaluation, the mean value of both sides was used.

The curl-ups (Figure 8 B) were started lying on the back, legs turned up, and arms slightly in the air. Without momentum, the test person had to sit up and then lay down again completely. A curl-up was valid if the test person managed to reach the top and completely sit up. The number of curl-ups indicates the test person's abdominal strength. For the evaluation, the maximum number of repetitions was taken.

The mobility and strength of the lower back (trunk lift, Figure 8 C) were measured out of the prone position. Patients placed both palms of the hand under their thighs and lifted their upper body as far as possible. The distance between the chin, when looking down, and the floor was set as a parameter. Two tests were carried out for the trunk lift and the better result was used for statistics.

The sit and reach (Figure 8 D) test was used to document the mobility of the back muscles of the hamstrings. Patients had to extend one leg, place the other at an angle at the level of the knee, and stretch forward as far as possible with both hands over the extended leg. For better measurability, a box was used as an aid to ensure that the leg was stretched and to create a 90° angle in the ankle joint. A negative result was obtained if they did not reach the tips of the toes whereas a positive result was obtained if the fingertips reached beyond the tips of the toes. For calculations, the mean of both sides was used.

The push-ups (Figure 8 E) were performed on the toes; hands were pointing forward and located approximately under the shoulders. A push-up was correctly performed and counted when the patient showed a clear bending and extension of the elbows, keeping the torso straight. This test aims to measure upper body strength. Maximum count was used for statistical analyses.

In the first paper, the raw values were used.[92] For rToF patients,[93] z-scores already existed and a total z-score was calculated.

Detailed specification of FITNESSGRAM tasks				
Test	**Skill**	**Task**	**Assessment**	**Impression**
Shoulder stretch	Upper arm and shoulder girdle flexibility	Reaching down the back with one fist over the shoulder, reaching up the back with the other fist trying to bring the fists together, then switching arms. Avoid hollow back.	Distance between the two forefingers is scored with negative values in cm to the nearest 1 cm. When forefingers of the fists touch or overlap, test is scored with zero. One attempt is permitted per site.	 A
Curl-up	Abdominal strength and muscular endurance	Lying in supine position with flexed knees at an angle of around 140° and feet placed on the mat. The arms are stretched out on the level of the knees, while the upper body moves slowly towards the knees and afterwards back to the mat	The exercise should be performed until exhaustion, a maximum of 75 repetitions or until the second formal correction is made. Formal corrections are necessary in case of feet leaving the mat or if pauses are made	 B
Trunk lift	Trunk extensor strength and flexibility	Lying in prone position with toes pointed and hands under the thighs, then lifting upper body to maximum of 12 inches (30.5 cm) without bouncing movements while looking towards the floor	The patients should have their head extended from the spine and look straight to the mat, while lifting the upper body slowly. Distance between the patient's chin and the mat is assessed during pause in the the lifted position.The patient has two trials and the better one is recorded	 C
Sit and reach	Hamstring flexibility	Sitting on the floor with one leg fully extended and foot flat against a box. The knee of the other leg flexed and foot placed on the mat. Moving the upper body with arms stretched towards the toes as far as possible, then switching legs	Scale is fixed on top of the box with the zero at the edge of the box. Without bouncing, upper body moves three times with stretched arms and palms towards the box. During the third movement, the position should be held for assessment to the nearest 1 cm. Positive values are recorded when the end of the fingers reach further than the toes, negative values are recorded when the end of the fingers do not reach the toes	 D
Push-up	Upper body strength and muscular endurance	First adopting a prone position, with arms straight and under the shoulders. Back and legs have to be also straight. Then pushing up and down with arms till elbows are flexed to an angle of 90° until exhaustion.	The exercise should be performed until exhaustion or until a correct performance is no longer possible. Formal corrections are allowed if extending arms fully straightened or flexing arms not achieving a 90° angle in the elbows. The score of valid repetition is the number recorded for push-ups.	 E

Figure 8: Detailed description of the health-related physical fitness test battery

The illustration was taken from Hock et al.,[92] online supplement

HEALTH-RELATED QUALITY OF LIFE

Health-related quality of life (HRQoL) was tested via the KINDL-R questionnaire. The questionnaire consists of 24 items, in six different domains (physical well-being, emotional well-being, self-esteem, family, friends, school), and calculated out of these a total HRQoL score with a Likert-scale.[58,54]

The total score reaches from zero (worst) to 100 (best). Results were compared with a cohort of peers, recently tested.[68,94]

ARTERIAL STIFFNESS

To measure arterial stiffness, peripheral and central blood pressures were used. It was assessed using an oscillometric device (Mobil-O-Graph, I.E.M. Healthcare, Stolberg, Germany).[87,68] Patients were tested after a rest of five minutes in a supine position with a fitting cuff (depending on the circumference of patients' upper arm). Central systolic blood pressure, a surrogate of arterial stiffness, was calculated automatically with the ARC Solver Algorithm (Austrian Institute of Technology, Vienna, Austria) based on the recorded brachial pulse waves.[87]

4.3 VOLUME-ORIENTED INSPIRATORY BREATHING TRAINING

Before the inspiratory volume-oriented breathing training began, the patients received instruction in the use of the device and written instructions for use at home. The training should be carried out daily with 2-3 sessions of 10-30 repetitions each. Once a week the study supervisor (Julia Hock) contacted the patients. The progress of the training was recorded and possible questions about the device or application were answered. Besides, adverse events were documented. During the first two weeks, the patients maintained the volume they had in the beginning, to get used to the regular training. The breathing training was performed using the Coach2® Incentive spirometer lung trainer (Smith Medical ASD Inc., Minneapolis, MN, Figure 9).

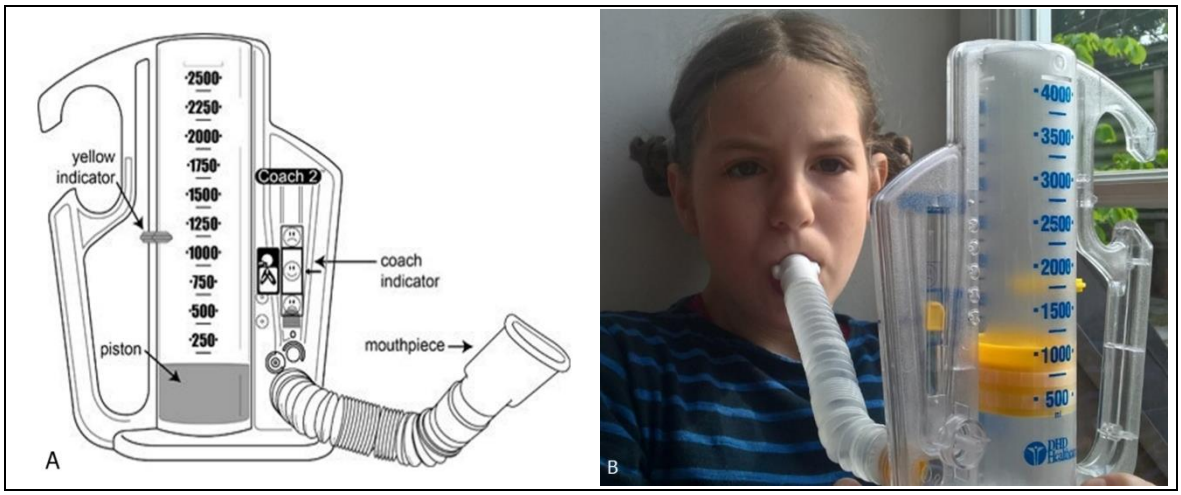

Figure 9: Coach2® Incentive spirometer lung trainer and a study participant on training

A: https://i.pinimg.com/600x315/89/2d/50/892d508c4948e908d4c8ef4dfd5496a3.jpg
B: all rights reserved by J. Hock

SPIROMETRY

The lung volumes were measured just before the patients underwent the CPET measurement to avoid possible effects of maximum exercise performance. For the study, the forced vital capacity (FVC) and forced expiratory volume within the first second (FEV1) were measured via the flow-volume curve (Figure 10).

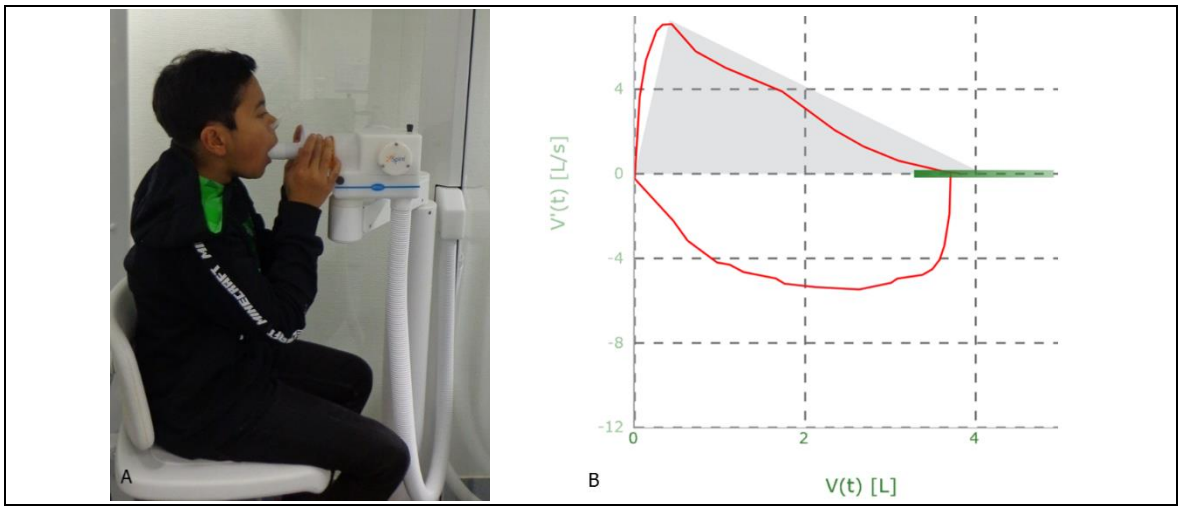

Figure 10: Measurement of spirometry and graphical result

A: all rights reserved by J. Hock
B: flow-volume curve; V'(t) [L/s]: flow over the time in liter per second, V(t) [L]: Volume over time in liter

The tests were done following the American Thoracic Society (ATS) criteria.[95,80] To calculate z-scores, Global Lung Initiative (GLI) reference equations from 2012[96] were used.

BREATHING EXCURSION

The breathing excursion was measured in a supine position with a measuring tape at the height of the xiphoid.[86] The thoracic circumference of the patients was measured after maximum inspiration and expiration (Figure 11). This was performed twice, and the larger difference was used to calculate the breathing excursion.

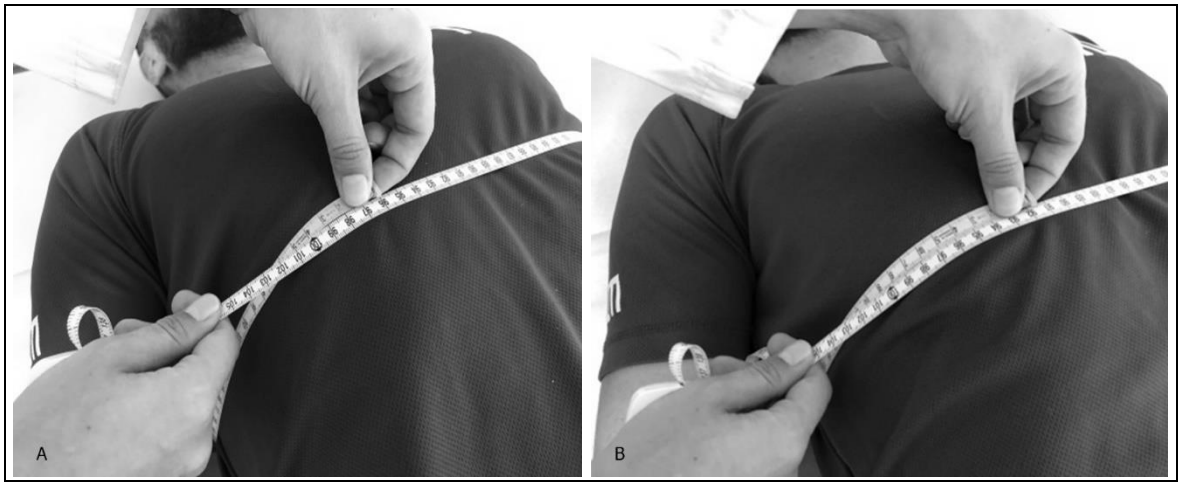

Figure 11: Measurement of breathing excursion (difference in centimeter)

A: maximal inhalation
B: maximal exhalation
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4.4 STATISTICS

Data are presented as mean ± standard deviation (SD).

In the first paper, focusing on children and adolescents with TCPC,[92] multivariable regression was used to show possible differences between patients and healthy reference cohorts (RCs)[94] in CPET, HRPF, and HRQoL

The second paper about patients with rToF[93] used the same RC for HRPF, but results were calculated with z-scores in HRPF. To classify the FITNESSGRAM® test, the results of the children with CHD, LMS values of the test results of the same RC were calculated using *R-Studio* (version 0.99.879, RStudio Incorporation) with the module extensions *gamlss* (version 3.4-8) and AGD (version 0.34). These analyses were done by Anna-Luisa Häcker as part of her Master's Thesis.

For the third paper first, a case number estimation was performed with G*Power. This estimation, based on a training study with ToF patients,[97] showed that 23 patients in each randomization group are needed (with a p-value of 5% and a power of >80%). Implementing a drop-out rate of 25%, at least 29 patients were needed. Therefore, 60 patients were recruited. For analyzing the randomized trial, the intention-to-treat analysis was used. Missing data were either replaced by the mean value of the respective group or, if applicable, the patients' value of the first investigation. An independent student's T-test was performed. To compare the training effect in all patients (data pre-training and post-training in all patients), the student's T-test for dependent samples was used. Here, only data from patients who filled in the questionnaire were used to and a correlation with training frequency was analyzed via Spearman's correlation. For calculations, SPSS 23.0 and 25.0 software (IBM Corporation, Armonk, NY, USA) were used. Two-sided p-values < 0.050 were considered significant.

4.5 PRIVACY POLICY

All patients and their parents were apprised, and written consent was given. Data is stored according to the privacy policy, which was valid in Germany for the years 2014-2018.
For the third paper, another written consent was used (DSGVO 2017). Potential study participants were recruited from the database of the *Deutsches Herzzentrum München*. They were first contacted via telephone and after a time of reflection of more than one day and after participation agreement, they were invited to an outpatient appointment at the *Deutsches Herzzentrum München*. All published papers are authorized by the journal to be reprinted in a dissertation by the first author. Written authorization is in the appendix. The third paper is currently under submission.

5 PUBLICATIONS

5.1 ARTICLE 1: FUNCTIONAL OUTCOME IN CONTEMPORARY CHILDREN WITH TOTAL CAVOPULMONARY CONNECTION – HEALTH-RELATED PHYSICAL FITNESS, EXERCISE CAPACITY AND HEALTH-RELATED QUALITY OF LIFE[92]

Authors: Julia Hock, Barbara Reiner, Rhoia C. Neidenbach, Renate Oberhoffer, Alfred Hager, Peter Ewert, Jan Müller

Journal: *International Journal of Cardiology*

DOI: 10.1016/j.ijcard.2017.11.092

SUMMARY

It is known that children and adolescents with a single ventricle heart after total cavopulmonary connection are often impaired in their functional outcomes. This study examines a collective of 78 young patients with a mean age of twelve years (12.0 ± 3.2 years of age, 21 females, July 2014 to October 2016). All patients underwent a five-task test battery to assess their health-related physical fitness (HRPF), a symptom-limited cardiopulmonary exercise test (CPET), and completed a questionnaire that queried their health-related quality of life (HRQoL). The assessment took place during their routine follow-up at the *Deutsches Herzzentrum München* after the patients and the guardians having signed a declaration of consent. Results from the examination of the study cohort were compared to a recently tested cohort of healthy subjects. For statistics, multivariable analyses were used (adjusted for sex, age, and BMI).

Results show that TCPC patients are significantly impaired in HRPF, peak oxygen uptake, and ventilatory efficiency. HRQoL did not differ significantly. Results support the generally accepted opinion of impaired peak $\dot{V}O_2$ and weakness in strengths and flexibility in children with TCPC. Low HRPF may yield to impaired motor competence and skills as well as to low exercise capacity. Early screening and possible treatments are recommended. However, it should be noted that HRQoL is like their peers. This may be influenced by coping-strategies or denial mechanisms. Patients are born with their disease and grow up with their limitations; they may not experience them as limitations.

SUBMISSION AND PUBLICATION

The article was submitted on December 15, 2016, to the *International Journal of Cardiology* by the first author. On October 22, 2017, the revised form was received and on November 27, 2017, the manuscript was accepted.

CONTRIBUTION

Jan Müller was the principal investigator of the study. Julia Hock was responsible for collecting the data with Barbara Reiner and Rhoia C. Neidenbach. Julia Hock analyzed the data herself with help from Jan Müller. She wrote the manuscript and, after the co-authors' review, submitted it to the *International Journal of Cardiology*. Further requirements (review) she composed together with Jan Müller.

Introduction

About 1% of all alive new-born children have a congenital heart disease (CHD) and about 3% of them are born with an univentricular heart [1]. Unfortunately, those patients are not amenable to biventricular repair but nonetheless have to undergo a three staged palliative surgical procedure to ensure survival [2, 3]. The final step is the total cavopulmonary connection (TCPC). After completion the venous blood is passively conducted to the lungs through an extracardial conduit or lateral tunnel, bypassing the right heart structures. After oxygenation, the blood pours into the remaining single ventricle that drives the systemic circulation.

Albeit functional mid and long-term outcomes improved over the past decades due to surgical progress and medical aftercare, children with TCPC still depict impaired motor development in motor skill [4], limited exercise capacity[5] and reduced health-related quality of life (HRQoL) [6]. In fact, neurodevelopment is impaired in all kinds of children with CHD already in infancy [7]. But those early neurological limitations, especially in severe CHD, are tracked from infancy into childhood and adolescents where they also become obvious as limitations in motor development, motor skills and health-related physical fitness (HRPF) [8-10]. In addition to the single ventricle morphology, neurodevelopmental and motoric impairments contribute to the diminished exercise capacity of these patients [11]. Those physical limitations may also affect the HRQoL since some studies report lower HRQoL [6, 12], whereas others show equal or even better HRQoL outcomes [5].

In front of this background the aim of this study was to investigate HRPF as a further evidence for motor development of children with TCPC, their exercise capacity and present HRQoL in comparison to healthy counterparts.

Patients and Methods

Study subjects

We included 78 children and adolescents (12.0 ± 3.2 years, 21 female) between 6 and 18 years with an univentricular heart after TCPC who had a routine follow-up appointment in our department between July 2014 and October 2016. All of them were free from syndromes, acute infects and able to exercise.

Patients' age at TCPC surgery was 2.3 ± 1.5 years. 69 patients had an extracardial connection and 9 a lateral tunnel. Their general type of CHD was hypoplastic left heart (27 patients), double inlet left ventricle (12 patients), tricuspidal atresia (13 patients), malposition of the great arteries (10 patients), atrioventricular anomaly (5 patients), hypoplastic right

heart (4 patients) and miscellaneous (7 patients). 34 TCPCs had a right systemic ventricle, 37 a left one and in 7 a dominant ventricle could not be defined.

Healthy controls (n=1650, 12.6 ± 2.4 years, 49% female) were obtained from studies recently conducted in several Bavarian schools. Several data from the reference studies has already been published elsewhere [13, 14]. With respect for participation in the investigation the inclusion in each analyses can be seen in Figure 1. Not all of included participants finished all tests. This was because of lack of time, fully booked capacity (outpatient) or further appointments. Written informed consent was obtained from all participants and their guardian. The study was approved by the local ethical board of the Technical University of Munich (project number: 314/14).

Health-Related Physical Fitness (HRPF)

Patients and healthy controls performed a motor test with five tasks. To asses upper-body strength they performed maximum repetitions in curl-ups and push-ups. Complete sitting up in curl-ups and at least 90° flexion in elbows in push-ups were required to be counted. The exercise was stopped after the second invalid execution. Flexibility was tested by shoulder stretch (distance between pointers' knuckles behind the back having a fist) and sit and reach (distance fingertips to toes, sitting), whereas trunk lift (distance chin to the ground) measured trunk extensor strength and flexibility. Shoulder stretch, as well as sit and reach, were performed separately for each side. Trunk lift was performed twice and the best value was recorded. The test battery was based on the Fitnessgram® [15]. More detailed instructions can be accessed from the online supplement. For analyses the mean of the left and right-sided test in shoulder stretch and sit and reach were used.

Cardio-pulmonary exercise test (CPET)

Exercise capacity was assessed with a symptom-limited cardio-pulmonary exercise test (CPET) on a bicycle in upright position with a rampwise protocol as it is routine in our institution [16]. Subjects' peak oxygen uptake ($\dot{V}O_2$ peak) was defined as the highest mean uptake of any 30 second time interval during exercise. Peak workload was described as maximum value in watt which the subjects reached when terminating the test. The estimated ventilatory efficiency $\dot{V}_E/\dot{V}CO_2$) represents how much liter of air patients have to exhale (volume of expiration $\dot{V}_E$) to eliminate one liter of CO2 ($\dot{V}CO_2$). The slope was calculated manually with the V-slope method according to Beaver et al. [17] and corrected by the $\dot{V}_E/\dot{V}CO_2$ curve. Ventilatory efficiency was displayed as $\dot{V}_E/\dot{V}CO_2$ slope confined to the linear part of the curve, excluding values beyond the respiratory compensation point [18].

Health-Related Quality of Life (HRQoL)

To estimate the HRQoL we used the KINDL-R since it is a common used questionnaire and sufficiently validated [19, 20]. It has 24 items, four for each of the six domains inquiring for the behavior and feelings during the last week's period. The questions can be answered on a 5-point Likert scale (never, seldom, sometimes, often and always). The results in the 24 items are summed up and calculated into a total score. The finally converted HRQoL scores range from 0 (worst) to 100 (best) whereas higher value indicates a better HRQoL.

Data analyses

Descriptive data was expressed in mean values and standard deviation (mean ± SD).
Means' differences between the patients and healthy controls were first analyzed via Student's t-test for independent samples. Second, since TCPC and healthy controls differ in anthropometrics (Table 1), multivariable regression was used to adjust for sex, age and BMI.
All analyses were performed using SPSS 23.0 software (IBM Corp., Armonk, NY, USA). Two-sided p-values <.050 were considered significant.

Results

Crude comparison of patients with TCPC and healthy controls is outlined in Table 2.
Of all TCPC patients 96.2% (n=75) finished the test battery for HRPF, 52.6% (n=41) completed a CPET and 79.5% (n=62) filled in the KINDL-R questionnaire.
In multivariable regression (Table 3), adjusted for sex, age and BMI, the impairments in all domains of HRPF became obvious. In terms of strength TCPC achieved just 45.4% of the mean curl-ups of healthy controls (Beta=-12.4, p<.001) and 71.7% in push-ups (Beta=-2.6, p=.010). In flexibility TCPCs' results were 7.5 cm worse in shoulder stretch (p<.001), 4.7 cm worse in sit and reach (p<.001) and they reached 65.5% of controls' mean in trunk lift (Beta=-8.5, p<.001).
Peak oxygen uptake was limited to 77.7% (Beta=-9.4; p<.001) compared to healthy peers. TCPC reached 34.8 ± 7.5 ml/min/kg whereas controls had 42.1 ± 8.4 ml/min/kg (p<.001). Also in peak workload TCPC achieved only 68.9% (Beta=-51.5, p<.001). Ventilatory efficiency, measured as $\dot{V}_E/\dot{V}CO_2$ slope, was impaired (healthy: 27.5 ± 2.9 vs. TCPC: 31.6 ± 3.3, p<.001) and after correction 4.4 points higher on average.
Regarding HRQoL the adjusted regression showed no difference (p=.184) between TCPC and healthy peers. There were no significant different in all functional parameters when comparing patients with a systemic right ventricle to those with a left one.

Discussion

This study showed that children and adolescents after TCPC still have functional limitations with regards to HRPF and exercise capacity. Their HRQoL, on the other hand, does not differ from healthy subjects.

Health-Related Physical Fitness (HRPF)

Already in infancy fine and gross motor skills of patients with CHD are insufficiently developed and the degree of impairment worsens with the severity of the defect [21]. Contributing factors for this early impairment are amongst other open heart surgery [7], time of deep hypothermic circulatory arrest, number of hospitalizations and time spent in the intensive care unit [22]. Patients with TCPC comprise more or less all of those factors. But also inborn neurological defects are associated with univentricular heart [23, 24]. It is therefore not surprising that limitations in gross and fine motor skills in infancy are tracked into childhood and adolescence where they are measured as complex limitations in HRPF and later on in motor competence. Other studies like Holm [8] and Bjarnason-Wehrens and coworkers [25] exhibited impaired motor competence or skill. Additionally we found restrictions in terms of upper-body strength, and shoulder, hamstrings and trunk extensor strength and flexibility. Other studies on HRPF as we have measured it are rare and controversial in their outcome. One study from Zaqout and collegues [10] recently published showed that boys with repaired CHD show less upper body strength and speed but not limitations in flexibility. Whereas girls performed better in lower muscular strength and showed no difference in speed and flexibility to healthy girls. However, their cohort did not include patients with Fontan-circulation. Contrary Longmuir and colleagues[9] found impairments in flexibility (sit and reach) but not in hand-grip strength in TCPC patients. Nevertheless, TCPC patients seem to have an 11-fold risk to develop severe deficits in motor competence [8]. The reasons are multifactorial and it is too simple to reduce them to parental overprotection and restrictions in daily activity. Indeed, that are contributing factors that have to be faced by the medical doctors, exercise physiologists and maybe also psychologists by likewise counselling parents and children, giving appropriate exercise advices and encouraging to an active lifestyle. Other limitations are the result of multiple thoracotomies which lead to chest wall and thorax incompliance and cause muscular imbalance and tension [26]. They will not vanish spontaneously. Physiotherapy and motor training are the significant treatment options and beneficial effects of motor training has already been proven [27, 28]. Otherwise limitations will further be tracked into adulthood and contribute

to a reduction in exercise capacity with peak oxygen uptake as the most important functional outcome measure in adults with CHD.

Finally, it should be mentioned that a study from Longmuir and colleagues[9] showed similar grip strength in TCPC patients compared to controls. Capturing hand-grip strength obviously not mirrors HRPF or motor development, but hand-grip strength is associated with generalized muscle strength [29] and has shown to be predictive for survival [30] and should therefore be part of further investigations in CHD.

Exercise capacity

Like shown in almost all studies of patients with older and recent types of Fontan circulation or TCPC [5, 11]. exercise capacity was also reduced in our TCPC cohort to 77.7% compared to our healthy subjects. Moreover, peak workload and ventilator efficiency were also diminished among our patients. Since only one ventricle drives the circulation, the passive pulmonary perfusion leads to a reduction in preload [31, 32]. Ventricular dysfunction and chronotropic impairment also fail to increase cardiac output under exercise [33]. But compared to our study cohort published almost eight years ago [5]. peak oxygen uptake has increased markedly from 59.7% to 77.7% in the recent cohort. We also noted that phenomenon in a more recent report in various CHD [34] and speculated that the better exercise capacity today is the result of more and tailored recommendations for physical behavior and exercise. Encouragement to physical activity in younger cohorts may also have contributed that most of the children with CHD are not limited in their submaximal exercise performance anymore [34]. But even though activity and exercise capacity are positively associated [35], Duppen and colleagues [36] failed to show if a 12-week aerobic exercise training program increases exercise capacity in Fontan patients. Lack of an increase in stroke volume due to preload impairment in the Fontan circulation might be a possible reason for the missing training progress. Nevertheless, they also conclude that a long-term training may show benefits and the absence of harm for the patients in their study reconfirms to stick to the guidelines for physical activity in patients CHD.

Health-Related Quality of Life

In our study HRQoL did not significantly differ from healthy peers, which is in good agreement to several investigations regarding HRQoL in TPCP or Fontan patients [37]. However, there are other studies reporting on lower HRQoL in children with TCPC [12, 38]. But with respect to their findings, many of those have methodological limitations like a small sample size, lack of control group, or outdated reference values established years or even decades ago. That becomes a relevant issue when considering that HRQoL underlies era and environmental effects [19, 20]. The fact that we have an actual control group from the same area and a relatively huge sample size in control and TCPC group strengthens our findings towards a good HRQoL. The possible reasons are multiple discussed and range from coping-strategies, denial mechanism, parental bonding and family enrolment up to the sense of coherence as a possible pathway [16, 39, 40]. However, maybe the reason is much simpler, and owed to the congenital nature of the disease that children grew up with their limitations and, therefore, did not experience them as those. Striving to clarify the inconsistency in HRQoL research in CHD and to figure out pathway further, especially qualitative, research is needed.

Conclusion

Patients with TCPC still present impaired HRPF and exercise capacity whereas HRQoL is similar to healthy peers. Since low HRPF may yield to worse exercise capacity early screening is recommended and needs to be treated if necessary.

Limitations

Unfortunately, not all of the test could be performed by all patients due time issues and usability of resources. However, since that happened by chance, we did not expect a sampling bias. This study refers to patients with TCPC that are in regular aftercare in a tertiary center that recommends physical activity very liberally. Both, proper medical management and the promotion of physical activity, may present a positive subgroup.

The possible influenced of physical activity on the functional outcome in general could not be ruled out since it was not assessed in the cohort. Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2017.11.092.

Acknowledgment

No conflict of interest.

Funding

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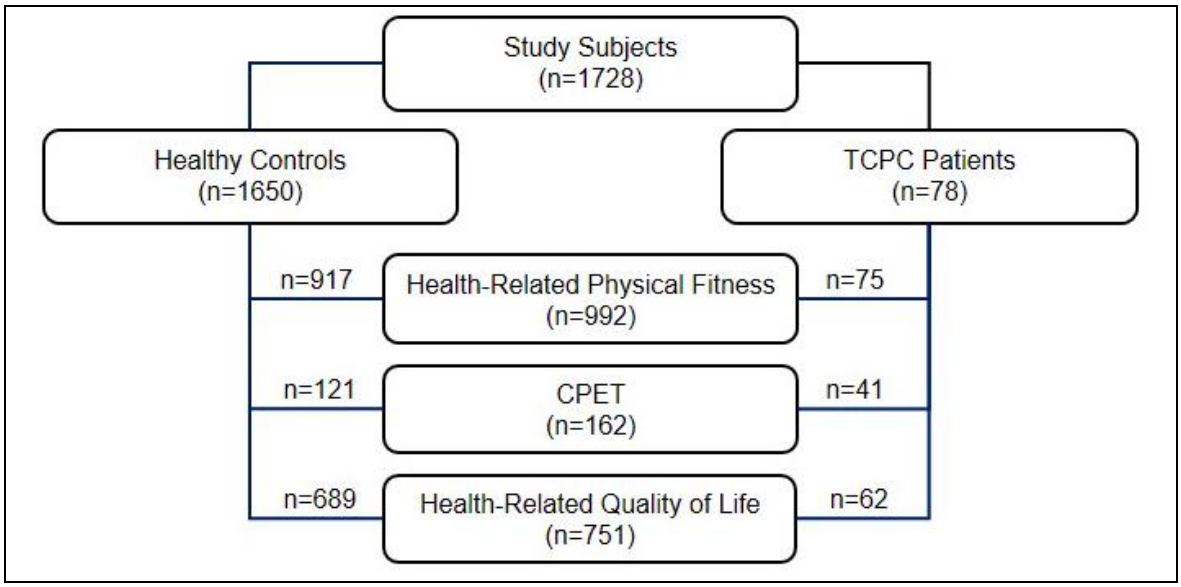
Figures

Figure 1: Subjects inclusion



TCPC: total cavopulmonary connection, CPET: cardio-pulmonary exercise test

Tables

Table 1: Study characteristics

	Healthy Controls (n=1650)	TCPC Patients (n=78)	p-value*
Sex (female)	807 (48.9%)	21 (27.0%)	**<.001**
Age (years)	12.6 ± 2.4	12.0 ± 3.2	.078
Body weight (kg)	47.0 ± 14.2	39.1 ± 14.5	**<.001**
Body Length (cm)	155.0 ± 13.6	145.2 ± 18.7	**<.001**
Body mass Index (z-score)	0.04 ± 1.05	-0.27 ± 0.86	**.003**

*Chi-Square test or Student's t-test for independent samples, significant with p<.050

Table 2: Comparison of TCPC patients with healthy controls with regard to health-related physical fitness, exercise capacity and health-related quality of life.

Health-Related Physical Fitness (n=992)			
	Healthy Controls (n=917)	**TCPC Patients (n=75)**	**p-value***
Curl-Ups (maximum repetition)	22.7 ± 17.2	11.6 ± 13.9	**<.001**
Push-Ups (maximum repetition)	9.2 ± 9.1	8.3 ± 8.4	.413
Shoulder Stretch (distance in cm)	-8.9 ± 5.6	-16.3 ± 6.3	**<.001**
Sit and Reach (distance in cm)	0.1 ± 7.5	-5.4 ± 8.1	**<.001**
Trunk Lift (distance in cm)	24.6 ± 6.2	15.5 ± 5.8	**<.001**
CPET (n=162)			
	Healthy Controls (n=121)	**TCPC Patients (n=41)**	**p-value***
$\dot{V}O_2$ peak (ml/kg/min)	42.1 ± 8.4	34.8 ± 7.5	**<.001**
peak Workload (watt)	165.7 ± 41.3	125.2 ± 45.2	**<.001**
Ventilatory Efficiency ($\dot{V}_E/\dot{V}CO_2$ slope)	27.5 ± 2.9	31.6 ± 3.3	**<.001**
Health-Related Quality of Life (n=751)**			
	Healthy Controls (n=689)	**TCPC Patients (n=62)**	**p-value***
Total score in KINDL	75.7 ± 10.1	79.0 ± 8.3	**.011**

TCPC: total cavopulmonary connection, CPET: cardio-pulmonary exercise test, V̇O2 peak: maximal ventilated oxygen, V̇E/V̇CO2 slope: ventilatory expiration of one liter CO2 per minute

* Student's t-test for independent samples, significant with p<.050.
** Score between 0-100 with "0" as worst and "100" as best.

Table 3: Multivariable regression models for subscales of health-related physical fitness, exercise capacity and health-related quality of life, adjusted for sex, age and BMI

Health-Related Physical Fitness (n=992)					
	Beta ± SE	**% to norm****	**β**	**R^2_{u}**	**p-value***
Curl-Ups (maximum repetition)	-12.4 ± 2.00	45.4	-.185	0.150	**<.001**
Push-Ups (maximum repetition)	-2.6 ± 1.02	71.7	-.074	0.199	**.010**
Shoulder Stretch (distance in cm)	-7.4 ± 0.69	-	-.318	0.173	**<.001**
Sit and Reach (distance in cm)	-4.7 ± 0.90	-	-.159	0.116	**<.001**
Trunk Lift (distance in cm)	-8.5 ± 0.74	65.5	-.331	0.194	**<.001**
CPET (n=162)					
	Beta ± SE	**% to norm****	**β**	**R^2_{u}**	**p-value***
$\dot{V}O_2$ peak (ml/kg/min)	-9.4 ± 1.16	77.7	-.463	0.527	**<.001**
peak Workload (watt)	-51.5 ± 6.12	68.9	-.490	0.513	**<.001**
Ventilatory Efficiency ($\dot{V}_E/\dot{V}CO_2$ slope)	4.4 ± 0.57	116.0	.540	0.309	**<.001**
Health-Related Quality of Life (n=751)					
	Beta ± SE	**% to norm****	**β**	**R^2_{u}**	**p-value***
Total score in KINDL	1.5 ± 1.28	102.8	.042	0.093	.233

TCPC: total cavopulmonary connection, CPET: cardio-pulmonary exercise test, $\dot{V}O_2$ peak: maximal ventilated oxygen, $\dot{V}_E/\dot{V}CO_2$ slope: ventilatory expiration of one liter CO_2 per minute

R^2: explained variance, SE: standard error, $_{u:}$ entire model.
* Significant with p<.050.
** Compared to mean of Table 2.

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5.2 ARTICLE 2: FUNCTIONAL OUTCOME IN CONTEMPORARY CHILDREN AND YOUNG ADULTS WITH TETRALOGY OF FALLOT AFTER REPAIR[93]

Authors: Julia Hock, Anna-Luisa Häcker, Barbara Reiner, Renate Oberhoffer, Alfred Hager, Peter Ewert, Jan Müller

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SUMMARY

The congenital heart disease (CHD) tetralogy of Fallot is the most common cyanotic CHD. Today, newborns reach adulthood and even old age. This study investigates the current state of functional outcomes in patients with repaired tetralogy of Fallot (ToF). A total of 106 patients with a mean age of 13.5 ± 3.7 years (40 females) were included. All underwent a symptom-limited cardiopulmonary exercise test (CPET), a battery of five tasks to assess their health-related physical fitness (HRPF). Arterial stiffness (pulse wave velocity, PWV, and central blood pressure, cBP) was measured using Mobil-O-Graph. All patients and their guardians signed consent of agreement before being included. Results were compared to a recently tested cohort of healthy children. For statistics, test results of the children with ToF, LMS values of the test results of the healthy children (HC) were calculated using *R-Studio* (version 0.99.879, RStudio Incorporation) with the module extensions *gamlss* (version 3.4-8) and AGD (version 0.34).

Compared with healthy children, patients with ToF showed lower predicted $\dot{V}O_2$ peak, impaired ventilatory efficiency, chronotropic incompetence (inadequate heart rate compared to peers), and reduced HRPF. Arterial stiffness did not differ compared to the reference.

Early screening of rToF patients may lead to early treatment, and this may prevent patients from progressing to disabilities. They may have reached their ”cardiac maximum” and further training is needed to increase exercise capacity.

Peripheral and central blood pressures are not increased, which may be due to the tetralogy of Fallot anatomical nature and its surgical repair; on the other hand, the patients benefit from good tertiary care.

SUBMISSION AND PUBLICATION

The article was submitted on December 33, 2017 to the Journal *Archives of Disease in Childhood* by the first author. On May 30, 2018, the revised form was received and on June 11, 2018, the manuscript was accepted.

CONTRIBUTION

Jan Müller was the principal investigator of the study. Julia Hock was responsible for collecting the data with the co-authors Anna-Luisa Häcker and Barbara Reiner. Julia Hock analyzed the data herself with help from Jan Müller. She wrote the manuscript and, after the co-authors' review, submitted it at the *Archives of Disease in Childhood*. Further requirements (review) she composed together with Jan Müller.

Introduction

According to a recently published study 107.6 per 10,000 live births in Germany are born with a congenital heart disease (CHD).[1] 2.5% of these newborns suffer from Tetralogy of Fallot (ToF). In addition, 0.6% have pulmonary atresia (PA) with a ventricular septal defect (VSD) and 1.0% a double outlet right ventricle of Tetralogy type (DORV-ToF). All three are grouped as ToF in the following. Within the last decades, survival of patients with CHD has tremendously increased and the focus in treatment has shifted from a focus only on survival to a broader functional assessment of daily living activities. Although studies show good survival in patients with ToF, undergoing surgery in infancy leaves patients with functional limitations throughout life.[2] These limitations in the functional status include arrhythmia,[3] health-related physical fitness (HRPF)[4,5], limited exercise capacity[6,7] and also reduced health-related quality of life.[8] Recent studies also suggest increased arterial stiffness in ToF patients.[9,10] Both, arterial stiffness[11] and exercise capacity[12] have shown to be good predictors for mortality and morbidity in the general population. More than that, the same relationship seems to hold true for exercise capacity in patents with CHD and ToF in particular.[7] Concerning these limiting factors above, the present study aims to investigate contemporary children, adolescents and young adults with ToF after repair, in regard to their exercise capacity, HRPF and arterial stiffness and compare them to a healthy cohort.

Methods

Design and Setting

The study protocol started in 2014 with the aim to prospectively assess functional outcome measures in children with CHD. That includes cardiopulmonary exercise testing, HRPF, arterial stiffness and quality of life. The study is still ongoing. Patients and guardians were recruited during their regular appointment at the outpatient clinic of the German Heart Center Munich. All tests were subsequently performed during that outpatient visit. The local ethical board of the Technical University of Munich approved the study. Written informed consent was obtained from all participants and their guardians.

Patients

In this study, a sample of 106 patients (13.5 ± 3.8 years, 40 female) between 5 and 21 years with ToF after repair were included (Table 1). All of them had an appointment at the German Heart Center in Munich due to their routine follow-up from July 2014 to January 2018. None of them suffered from any symptoms, acute infects or exercise restrictions.

Median age of surgical correction was 8.0 [4.0; 13.0] months. Fifty-four (50.9%) patients underwent a repair with a transvalvular patch, while in 31 (29.5%) any kind of conduit and in eleven (10.4%) a subvalvular patch was used. Further seven (6.6%) patients got their repair omitting any right ventricular outflow tract patch. In five (4.7%) patients the type of corrective surgery remained unknown because surgery was performed abroad and the surgical reports were not available.

Their underlying CHD distribution was as follows: 83 (78.3%) with a Tetralogy of Fallot, 17 (16.0%) with ToF+PA and eight (7.6%) suffered from a DORV from the Fallot-Type (DORV-ToF) without transposition of the great arteries. In addition, two patients had a pacemaker. 72.6% (n=77) of all patients completed a CPET. In 94.3% (n=100) ToF patients a HRPF-score was estimated and 68.9% (n=73) underwent an arterial stiffness measurement. Seven patients completed one, 53 two and 46 patients all three tests.

Healthy patients' data were used from published[13,14] and unpublished data (n=1700, 12.8 ± 2.6 years, 49% female), previously collected from local schools by the same study team using the same protocols.

Study protocol

Cardio-Pulmonary Exercise Test (CPET)

Exercise capacity was assessed by a symptom-limited CPET on a bicycle in upright position with a ramp-wise protocol as it is routine in our institution.[15] Subjects' peak oxygen uptake ($\dot{V}O_2$ peak) is defined as the highest mean uptake of any 30 second time interval during exercise. Peak workload is described as maximum value in Watt achieved when terminating the test. The estimated ventilatory efficiency $\dot{V}_E/\dot{V}CO_2$ slope) represents the liter of air patients have to exhale (volume of expiration $\dot{V}_E$) to eliminate one liter of CO2 ($\dot{V}CO_2$). The slope was calculated manually with the V-slope method according to Beaver et al.[16] and corrected by the $\dot{V}_E/\dot{V}CO_2$ curve. Ventilatory efficiency is displayed as $\dot{V}_E/\dot{V}CO_2$ slope confined to the linear part of the curve, excluding values beyond the respiratory compensation point. Data is defined as valid when patients terminated the test with a respiratory exchange ratio greater than 1.0 to ensure metabolic exhaustion.[17] Reference values for $\dot{V}O_2$ peak for patients under 25 years of age were calculated according to Cooper and Weiler-Ravell.[18]

Health-related Physical Fitness (HRPF)

The test was based on the FitnessGram®[19] which has shown to be a valid and reliable measure of HRPF. It comprises five tasks: (1) maximum repetitions in curl-ups as well as (2) push-ups to assess upper body strength. After two failed attempts to perform the movement, the task was terminated, and the number of successfully completed repetitions counted. (3) Shoulder stretch (shortest distance between knuckles of the fists behind the back) and (4) sit and reach (sitting on the ground, one leg bent, distance fingertips to toes or beyond) were performed to assess flexibility separately for the left and right side. For statistics, the mean of the left- and right-sided test in shoulder stretch and sit and reach were used together. The last test (5) trunk lift (lying in prone position measuring distance between chin and ground) measured trunk extensor strength and flexibility; the better of two trials was recorded. Detailed information on test execution was recently published.[20]

Pulse Wave Analysis

Arterial stiffness was analyzed by pulse wave analyses using an oscillometric measurement device (Mobil-O-Graph®, IEM Healthcare, Stolberg Germany) as recently described.[21] Measurements were performed in supine position on the left upper arm after resting for five minutes. Cuff's size was adjusted individually to patient's arm circumferences. Central systolic blood pressure (cSBP) was indirectly estimated with the ARCSolver Algorithm (Austrian Institute of Technology, Vienna, Austria) based on the recorded brachial pulse waves. Its validation and reliability has been proven within several studies.[22]

Data analyses

Descriptive data is expressed in mean values and standard deviation (mean ± SD), median and interquartile range (median [IQ25; IQ75]), total numbers and percentage where appropriate.

For the healthy reference cohort, we used LMS-Method[23] for constructing normalised percentiles and and z-scores for children. The values were smoothed for HRPF with a Box-Cox transformation using R-Studio (version 0.99.879, RStudio Inc.) with the module extensions gamlss (version 3.4-8) and AGD (version 0.34) for all of the five exercises of the Fitnessgram. The total HRPF-score represents the mean of the five tasks exercises and was calculated if at least three of the tasks were executed.

Comparison between ToF and healthy controls (HCs) were made via Student's t-test for independent samples. To adjust for co-variates in the second step, a general linear regression model was fit to the data. For exercise capacity measures entered co-variates were

sex, age and body mass index (BMI). For arterial stiffness we controlled for BMI, heart rate, mean atrial blood pressure and hypertensive agents.21 Additionally, an Analysis of Variance (ANOVA) with Bonferroni post-hoc analysis was calculated estimating differences within the different heart diseases (ToF, ToF+PA, DORV-ToF) and surgical procedures (conduit, transvalvular, subvalvular, transatrial).

All analyses were performed using SPSS 23.0 software (IBM Corp., Armonk, NY, USA). Two-sided p-values < 0.050 were considered significant.

Results

Contemporary patients with ToF showed lower predicted "V" ̇O2 peak (ToF: 80.4 ± 16.8% vs HC: 102.6 ± 18.1%, P<0.001), impaired ventilatory efficiency (ToF: 29.6 ± 3.6 vs HC: 27.4 ± 2.9, P<0.001) and chronotropic incompetence (ToF: 169 ± 17 bpm vs HC: 190 ± 17 bpm, P<0.001) compared to HC (Table 1).

Total HRPF score was also reduced (ToF z-score: -0.65 ± 0.87 vs HC z-score: 0.03 ± 0.65, P<0.001) as well as almost all of the five tasks of the Fitnessgram (Table 2). Table 2 shows that patients performed worse (P<0.001) except for push-ups (P=0.497). There were no differences in SBP (P=0.065) and cSBP (P=0.217) between ToF and HC (Table 2). All of those findings hold true after adjustment for co-variates in a general linear model (see 'Data analyses' section).

There were no significant differences between miscellaneous heart defects and the type of corrective surgery. Nevertheless, there was a trend towards a lower $\dot{V}O_2$ peak in patients with DORV-ToF (n=6, 69.8 ± 9.5%), followed by ToF+PA (n=14, 77.3 ± 19.7%) and Tetralogy of Fallot (n=59, 88.6 ± 16.3%).

Additionally, the analyses showed a trend towards lower predicted $\dot{V}O_2$ in patients who received any kind of conduit (74.5 ± 15.8%, n=25). Those who received a transvalvular patch reached 82.4 ± 16.7% of predicted $\dot{V}O_2$ (n=34), subvalvular patched 85.3 ± 17.4% (n=11) and patients with transatrial patch reached the best result (86.7 ± 19.0%, n=6), although these results were not significant.

Discussion

Our data show that a contemporary cohort of children with ToF after repair, still have impaired exercise capacity and reduced HRPF, whereas peripheral SBP and central SBP did not differ from healthy controls.

Exercise capacity

Exercise capacity is a strong predictor for morbidity and mortality and especially for cardiovascular diseases[12] and it is still one of the most important functional outcome parameters in clinical aftercare. It should be used for risk stratification in patients with ToF.[7] In line with results of previous studies[7,24] contemporary patients with ToF have diminished exercise capacity with reaching only 77.8% of the predicted reference value. Also, peak workload and ventilatory efficiency were worse in comparison to controls and with a maximum heart rate of just 89.0% of the healthy (HC: 190 ± 29 vs. ToF: 169 ± 17 bpm) they still have some chronotropic incompetence.[25]

However, ventricular scarring in ToF is still a major concern and highly prevalent due to extensive incision and patching after corrective surgery.[26] That in combination with right ventricular volume overload contributes to a slow proceeding in heart failure and QRS prolongation.[27] Longer QRS duration is directly associated with limited exercise capacity[28] and patients having a right bundle branch block show lower peak heart rate.[29] So about 20 years after the outstanding studies from Gatzoulis[3], mechanoelectrical interactions are still the challenge to meet since Vehmeijer and colleagues[30] have shown that QRS duration and QRS fragmentation are strongly associated with sudden cardiac death, most prominent in ToF. Therefore, QRS duration and exercise capacity are still important substrates to monitor the risk of sudden cardiac death.[7]

Health-Related Physical Fitness (HRPF)

Previous studies have shown underdeveloped fine and gross motor skills in young children with CHD that worsen become worse with the severity of the CHD.[31] More recent studies still show that also motor development is impaired in patients with CHD, and ToF in particular.[4] Our findings are thereby in agreement with the results of preceding studies.

The etiology of decreased HRPF however has multifactorial reasons. Cardiopulmonary arrest during open heart surgery resulting in neurological sequels has shown to be the major cause for limitations in motor development and HRPF.[32-34] Moreover, number of hospitalizations, palliative surgery, microcephaly, days spent in intensive care and multiple thoracotomies are associated with impairments as well.[34] These multiple thoracotomies lead directly to chest wall and thorax incompliance and cause muscular imbalance and tension.[35] To make matters worse parental overprotection in childhood or unnecessary restrictions from medical doctors to participate in daily activity or sports[36] are causing limitations as well.

Consequently, if a toddler is already faced with some small retardation in motor development, it is likely that those limitations are tracked from childhood to adolescence and may even be present in adulthood and affect HRPF negatively. To avoid tracking of impairments, a comprehensive approach of medical doctors, exercise physiologists and maybe even psychologists are needed in the primary, secondary and tertiary care of patients. They need to give appropriate advices, promote active lifestyle and should not restrict physical activities unless there is a certain risk for sudden death from ventricular tachycardia.

Pulse Wave Analysis

Arterial stiffness at an early age is problematic due to its association to long-term mortality and morbidity.[37] Recently published research from our study group found that several diagnostic subgroups of CHD present stiffer vessels than their healthy peers, but not in patients with right heart obstruction.[21] The same holds true in the current study referring to ToF only.

In contrast to left heart obstruction a possible explanation for the normal stiffness in ToF patients is that the defect is located on the right heart side at the pulmonary system and not at the systemic circulation. During surgical repair, the aorta is not that much affected which is assumed the major reason for enhanced arterial stiffness.[38] Increased pulmonary arterial stiffening[39] might possibly become an issue in this cohort. Further studies should focus on that.

Nevertheless, structural abnormalities in the ascending aorta have been found in intraoperative biopsies in ToF patients.[40] However in this study[40] these abnormalities were primarily found in patients with ToF+PA or who underwent e.g. Blalock-Taussig shunt. Unfortunately with only 6.5% (17 of 106 patients) ToF+PA were underrepresented in our cohort. In order to estimate any increases in arterial stiffness within the different underlying CHD groups, further studies have to be conducted.

Conclusion

Children, adolescents and young adults with ToF (including ToF+PA and DORV-ToF) after repair show impairments in exercise capacity and HRPF. Since low HRPF may yield to worse exercise capacity, early screening for HRPF is recommended and needs to be treated if necessary.

Limitations

Unfortunately, not all of the tests could be performed by all patients due to time issues or usability of resources. However, since this happened by chance we do not assume a systematic sampling bias.
This study refers to patients with ToF after repair who are in regular aftercare in a tertiary center that recommends physical activity very liberally. Both, proper medical management and the promotion of physical activity, may present a positive subgrouping factors.

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Competing interests

None declared.

Patient consent

Parental/guardian consent obtained.

Ethics approval

The study was approved by the local ethic board of the Technical University of Munich (project number: 314/14).

Provenance and peer review

Not commissioned; externally peer reviewed.

What is known on this topic? – Patients with Tetralogy of Fallot after total repair are impaired in their exercise capacity. Additionally, physical fitness seems to be restricted.
What this study adds – Our current data shows that limitations in exercise capacity and health-related physical fitness are still present in a contemporary cohort of children with Tetralogy of Fallot. Fortunately, patients' arterial stiffness (peripheral and central systolic blood pressure) seems to not be detrimental.

Tables

Table 1: Study characteristics

	Healthy Controls (n=1700)	ToF Patients (n=106)	P-value*
Sex (female)	837 (49.2 %)	40 (37.7 %)	**<0.001**†
Age (years)	12.8 ± 2.6	13.5 ± 3.8	0.066
Body weight (kg)	47.6 ± 14.7	46.3 ± 17.3	0.418
Body height (cm)	155.5 ± 13.7	153.8 ± 18.1	0.361
Body mass Index (z-score)	0.04 ± 1.05	-0.35 ± 1.23	**0.003**

*Student's t-test for independent samples, significant with P<0.050, displayed in bold

†χ^2 test.

ToF: Tetralogy of Fallot after repair.

Table 2: Comparison of ToF patients with healthy controls in regard to health-related physical fitness, exercise capacity, arterial stiffness

Cardiopulmonary exercise test			
	Healthy Controls (n=120)	**ToF Patients (n=77)**	**P-value***
$\dot{V}O_2$ peak (% predicted)	102.6 ± 18.1	80.4 ± 16.8	<0.001
$\dot{V}O_2$ peak (ml/kg/min)	42.0 ± 8.1	33.1 ± 7.3	<0.001
Workload (watt/kg)	3.4 ± 0.7	2.6 ± 0.6	<0.001
Ventilatory Efficiency ($\dot{V}_E/\dot{V}CO_2$ slope)	27.4 ± 2.9	29.6 ± 3.6	<0.001
Maximum Heart rate (beats/min)	190.1 ± 29.5	168 ± 16.6	<0.001
Health-related Physical Fitness			
	Healthy Controls (n=914)	**ToF Patients (n=100)**	**P-value***
Health-related Physical Fitness Score (z-score)	0.03 ± 0.65	-0.65 ± 0.87	<0.001
Push-ups (z-score)	0.01 ± 1.05	0.13 ± 1.62	0.497
Curl-Ups (z-score)	0.04 ± 1.07	-0.45 ± 1.37	0.001
Trunk Lift (z-score)	0.07 ± 1.10	-1.32 ± 1.60	<0.001
Sit and Reach (z-score)	-0.01 ± 1.14	-0.72 ± 1.57	<0.001
Shoulder Stretch (z-score)	0.05 ± 1.18	-0.79 ± 1.29	<0.001
Pulse Wave Analysis			
	Healthy Controls (n=1569)	**ToF Patients (n=73)**	**P-value***
Peripheral systolic blood pressure (mmHg)	117.4 ± 9.9	114.6 ± 12.6	0.065
Central systolic blood pressure (mmHg)	102.8 ± 9.6	104.9 ± 12.4	0.217

*Student's t-test for independent samples, significant with P<0.050,
ToF: Tetralogy of Fallot after repair, $\dot{V}O_2$ peak: maximal ventilated oxygen, $\dot{V}_E/\dot{V}CO_2$ slope: ventilatory expiration of one liter CO_2 per minute, bpm: beats per minute

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5.3 ARTICLE 3: BREATHING TRAINING INCREASES EXERCISE CAPACITY IN PATIENTS WITH TETRALOGY OF FALLOT: A RANDOMIZED TRIAL[98]

Authors: Julia Hock, Julia Remmele, Renate Oberhoffer, Peter Ewert, Alfred Hager

Journal: (currently submitted)

DOI: none yet

SUMMARY

The physical performance of patients with repaired tetralogy of Fallot (rToF) is highly variable and averages about 85% of their peers. Reasons for these conditions can be due to irrational fears of doctors, parents, and teachers which lead to less sporting activity. Besides, many patients have decreased lung function, which may be important, since good lung function correlates with higher exercise capacity (peak oxygen uptake, peak $\dot{V}O_2$).

With the inspiratory volume-oriented breathing training that we applied, an improve patients' peak $\dot{V}O_2$ was investigated. Improved ventilation of the lungs may reduce the resistance in the pulmonary circulation, which in turn relieves the volume- and/or pressure-loaded to the right ventricle in many patients with rToF.

This study applied a home-based inspiratory volume-oriented breathing training. By strengthening the respiratory muscles and improving thoracic mobility, improvement in lung function, peripheral oxygen supply, and, consequently, better aerobic performance demonstrated by cardiopulmonary exercise test (CPET).

From February 2017 to November 2018, sixty patients (age at inclusion: 14.7 ± 4.8, range: 8-23 years of age, 39% female) participated in the study. All underwent spirometry (to measure FVC and FEV1) and a CPET (peak $\dot{V}O_2$), and breathing excursion was measured. They were randomized into immediate breathing exercise or a control group with training after a delay of six months. Patients were re-examined six months after randomization as well as after their training. In the first six months (intention-to-treat analysis) the training group exhibited a significant increase in exercise capacity, lung function, and breathing excursion. A significant correlation between training-frequency and improvement in all patients was observed.

This randomized controlled trial shows that a daily six-month inspiratory breathing training without an aerobic exercise component can increase rToF patients' peak $\dot{V}O_2$, lung function, and thoracic flexibility. Especially patients who cannot participate in exercise training due to for example living circumstances, co-morbidities, or anxiety may benefit from this training.

SUBMISSION AND PUBLICATION

This article is currently submitted.

CONTRIBUTION

Alfred Hager was the medical principal investigator of the study. Julia Hock and Alfred Hager were responsible for the study concept, ethical approval, and administrative support. Julia Hock invited the patients, collected, and analyzed the data herself. She wrote the manuscript and, after the co-authors' review, submitted it. Julia Remmele gave important advice in the testing battery (breathing excursion). Julia Remmele, Renate Oberhoffer, Peter Ewert, and Alfred Hager gave important feedback on the manuscript.

Introduction

Tetralogy of Fallot (ToF) is the most common cyanotic complex congenital heart disease [1]. Corrective surgery is recommended in infancy. Nevertheless, after surgical repair, the malfunction of the pulmonary valve or right ventricle is not rare. This includes, in particular, recurrent stenosis of the pulmonary valve, pulmonary valve regurgitation, dysfunction of the right and/or left ventricle, and arrhythmia, or sudden cardiac death [2]. Regular monitoring over the long term is recommended including cardiopulmonary exercise testing to objectify exercise performance and to detect deteriorations in the right heart function early [2, 3]. Exercise capacity of ToF patients is very variable and on average only about 85% of the peers of the same age [4]. Besides, patients' breathing function is affected and in many patients, even in young children [4], a restrictive lung function correlates with reduced exercise capacity [5]. Regarding this, it has been shown that controlled physical training can increase physical endurance capacity of children and young adults with ToF [6].

A few studies are dealing with breathing training in patients with congenital heart disease. Laohachai et al. [7] showed an improvement in muscle strength and breathing efficiency in patients with Fontan circulation. Fritz et al. [8] showed a significant increase in adult patients with Fontan circulation in oxygen saturation but not in exercise parameters. Both used inspiratory muscle training. Mereles et al. [9] showed a positive effect on exercise capacity via respiratory and exercise training in patients with various kinds of pulmonary arterial hypertension.

The current study tested the hypothesis, whether a home-based volume-oriented inspiratory breathing training increases exercise capacity, expressed as peak oxygen uptake. By improving thoracic mobility, improvement in lung function, and a more homogeneous alveolar oxygen supply is expected. By the Euler-Liljestrand-mechanism [10] this may lead to pulmonary vascular dilatation, improvement of lung perfusion, reduction of right heart afterload, and finally to improved exercise performance.

Methods

Study Design

The study was a prospective registered randomized non-blinded clinical trial on breathing exercises. The primary outcome was the improvement of exercise capacity (peak$\dot{V}O_2$), secondary outcomes included lung volumes and thoracic flexibility.

Patients

The patients' inclusion started in February 2017 and the last patient was randomized in November 2017.

The study population consisted of patients with repaired tetralogy of Fallot (ToF) including double-outlet right ventricle of Fallot-type and pulmonary atresia with ventricular septal defect from 8-25 years of age.

Exclusion criteria were obstructive lung function (FEV1/FVC z-score < -1.64), change in medication within the last three months, therapeutic catheterization within the last six month, heart-surgery within the last 12 month, planned surgery within the next 36 month, severe left heart failure (New York Heart Association classification, NYHA IV), frequent arrhythmia, a pacemaker or acute lung infection. Potential subjects were recruited from our Munich database for congenital heart defects. There were no public recruiting measurements. They were contacted via telephone calls, the information material was sent out and after some time of reflection (> one day), patients were invited to an outpatient appointment at our institution. At baseline, all underwent echocardiography, spirometry, breathing excursion, and a cardiopulmonary-exercise test. Of 75 invited patients, 60 were eligible and randomized. Thirty started their training immediately and 30 after six months (Fig. 1). All patients answered a questionnaire after their training which queries if and how often they did the respiratory training.

Outcome Measures

Cardiopulmonary exercise test

Patients had to undergo an exhausting (respiratory exchange ratio >1.0)[11] and symptom-limited cardiopulmonary exercise test (CPET) in an upright position on a bicycle. The highest running thirty-second-time interval of oxygen uptake during exercise was defined as peak oxygen uptake (peak$\dot{V}O_2$). Estimation of ventilatory efficiency ($\dot{V}_E/\dot{V}CO_2$ slope) was defined manually excluding the values after the respiratory compensation point. All subjects performed a customized ramp-wise protocol aiming at an exercise time of about 8-12 minutes. As reference values, the height-dependent calculations from Cooper et al. [12] were used and data were also expressed as a percentage of predicted (%predicted).

Spirometry

Forced vital capacity (FVC) as well as forced expiratory volume within the first second (FEV1) were measured just before the CPET to avoid any possible influence on the results due to possible better lung ventilation after maximum physical exertion. The test was done

following the ATS criteria [13, 14]. GLI 2012 references [15] were used to calculate z-scores.

Breathing excursion

Breathing excursion was measured in a supine position with a tape measure at the xiphoid level. Patients' thoracic circumference was measured after maximal inspiration and expiration. This was done twice, and the larger difference was used for the calculation of breathing excursion.

Randomization

Four sealed randomization letter sets were prepared by the Institute for Medical Information Technology, Statistics and Epidemiology, Technical University of Munich, block randomized for males/females, and <14/≥14 years of age. They were consecutively opened for every patient after informed consent and after all the baseline investigations.

Inspiratory Breathing Training

A volume-oriented inspiratory respiratory training was performed with the Coach2® Incentive spirometer lung trainer (Smith Medical ASD Inc., Minneapolis, MN). The device is CE marked for postoperative rehabilitation. It was already used in patients with chronic obstructive airway [16] and in patients with thoracic surgery in general to improve their lung re-expansion [17]. This device motivates the patient to a constant slow but long inspiration up to a certain inspiration volume without flow resistance. Exhalation is not controlled by the device.

Patients started the training with an inspiration volume of about 40% of their previous measured FVC (L) and trained every day in one to three sets with ten to 30 repetitions (following the producer's recommendations). This wide range was chosen since changes in the volume's increase take a long time to achieve and patients' training needs to be adapted also to guarantee personnel success (self-efficacy). Within the first two weeks, the patients maintained the volume they had in the beginning, and afterward, they adapted it individually with the guidance of the study's supervisor.

Before starting the training, patients were instructed in different breathing techniques and breathing training with the device.

Once a week the supervisor contacted all patients in training, following a call-protocol to get information about training progress, and adapted the inspiration volume individually. Possible adverse events were documented.

Statistical Analyses

In advance, case number estimation was performed. In a training study of patients with tetralogy of Fallot [18], an increase in $\dot{V}O_2$ of 2.14 ± 2.83 ml/kg/min in the training group and 0.35 ± 4.2 ml/kg/min in the control group was measured. Taking the standard deviation from this study and assuming an increase of 3 ml/kg/min for the improvements in hemodynamic is clinically relevant, a case number of 23 patients per randomization group is obtained with a $P<0.05$ and a power of >80%. With a drop-out rate of 25%, the inclusion of at least 29 patients per group is necessary. For this purpose, a total of 60 patients are to be recruited.

Data are expressed in mean ± standard deviation (dependent variables in Shapiro-Wilk test $P>0.05$). The randomized trial was evaluated via intention-to-treat analyses, whereby missing data were imputed by the initial value or, if no value was available, by the mean of the group. Data from the first six months was compared between the training group and the delayed training group (no training for this time) by an independent student's T-test.

For the correlation with training frequency, data of both groups were merged for their individual training period. Patients that did not finalize the training and the final questionnaire about training frequency were excluded. To compare data before and after training the student's T-test for dependent samples was used. To correlate the results with training days, Spearman's correlation was used. All analyses were performed using SPSS (version 25.0, IBM Corporation, Armonk, NY, USA) and a two-tailed probability value <0.05 was considered statistically significant for all tests.

This study was following the declaration of Helsinki and ICH Good Clinical Practice. The local ethical board of the Technical University of Munich approved the study (project number: 4/17S). The study was registered in the "Deutsches Register Klinischer Studien" with the number DRKS00011363. Written informed consent was given by all patients and, if needed, by legal guardians.

Results

Patients' characteristics of the primary and secondary training groups can be seen in Table 1.

Intention to treat analysis

Initial values did not differ in training (TG, primary training group) and control group (CG, secondary training group). In three patients, lung volumes were missed, and respective means of their reference group were used for both examinations. Two patients missed the

2nd examination and their values from the 1st examination were used. As shown in table 2 the training group achieved a significantly more favorable change peak $\dot{V}O_2$ (TG: 0.5 ± 3.4 vs. CG -2.1 ± 4.7 ml/min/kg, P=0.017), ΔFVC (TG: 0.17 ± 0.17 vs CG: 0.06 ± 0.15 L, P=0.010) and ΔFEV1 (TG: 0.14 ± 0.17 vs CG: -0.02 ± 0.16 L, P<0.001). Breathing excursion did not show significant improvements.

Correlation with training days/week in the intervention study

Of all patients, six patients were lost to follow-up because they discontinued the study (Fig. 1). Fifty-four (90%) patients completed the six-months training and filled in the self-reported training frequency questionnaire. Of these, only 16 patients (30%) trained seven days per week during the six months. Spearman's correlation shows a positive correlation in self-reported training days/week and Δ peak$\dot{V}O_2$ (r=0.282, P=0.039, Fig. 2). Merged data from both groups before and after training are shown in table 3.

Discussion

This study showed that inspiratory breathing training increases exercise capacity and lung volumes. The power of improvements depends on exercise frequency.

Only a few published studies consider inspiratory breathing training in patients with congenital heart disease. Laohachai et al. [7] treated 23 young Fontan patients with six-week inspiratory muscle training (IMT) which consisted of 30 minutes of training per day. Their non-randomized study showed improvements in ventilatory efficiency and resting ejection fraction in cardiac magnetic resonance imaging. The patient's exercise capacity and lung function (peak$\dot{V}O_2$, FVC, and FEV1) did not change with the training. A recently published paper from Fritz et al. [8] investigated adult Fontan patients. This study was randomized with 42 patients. They underwent a six-month IMT of three sets with ten to 30 repetitions per day. They also received weekly calls. In this study exercise capacity and lung volumes did not change. Only oxygen saturation at rest increased significantly.

Also, there is a prospective non-randomized pilot study [19] with 11 adult patients with Fontan circulation who underwent inspiratory muscle training for 12 weeks. They also reported only a trend in an increased peak$\dot{V}O_2$ and improved $\dot{V}_E/\dot{V}CO_2$ slope.

Nevertheless, these studies investigated a different, very complex congenital heart disease compared to the present study. Fontan patients' pulmonary blood flow is mainly driven by left heart suction forces and negative intrathoracic pressures during inspiration [8]. Patients with repaired tetralogy of Fallot have a biventricular circulation and after the repair, the pulmonary and circulatory is similar to "normal" ones [2]. The studies on Fontan patients

implement inspiratory muscle training which differs from the training in this study. They used devices with inspiratory resistance that primarily increased ventilator suction capabilities that might be useful in Fontan patients. The present study focused on volume training by deep inhalation using a different training device. We shifted to the new training modality because, first, the durability of the POWERbreathe device was not as expected, second, we saw two previously undiagnosed hiatal hernias in a program of about 100 patients with IMT that might have been pursued or worsened by the IMT, and third, the hemodynamics of Fallot patients is not dependent on the ventilator pump as it is the Fontan circulation. In the volume-oriented breathing training of the current study, the respiratory muscles are strengthened via deep inspiration, as well as thoracic mobility is improved, despite this could not be shown in our data. Lung volumes are increased leading potentially to better alveolar ventilation. This might improve alveolar ventilation and pulmonary perfusion and finally a right heart afterload reduction. We can only speculate on this physiologic pathway, but in the end, exercise capacity was increasing. Unfortunately, no MRI data about right ventricular function at exercise were measured to support the hypothesis of how the improvements in lung volumes result in better exercise capacity in this patient group.

Studies have already shown that there is a correlation between spirometry and exercise capacity [5]. By our randomized study, showing that volume-oriented breathing training improves exercise capacity, there is no proof that the reduced exercise capacity is not only associated with a reduced lung function, but it is also at least in part the result of a decreased lung function. Our volume-oriented inspiratory breathing exercise improves lung function and gives medical doctors and therapists of Fallot patients an option to escape from the status of bad lung function and bad exercise capacity. Furthermore, this study might focus our interest on the reasons for reduced lung volumes. Finally, it should be the aim to prevent impaired lung volumes. As the number of thoracotomies correlates with a reduced lung volume [20] avoiding thoracotomies by catheter interventions like percutaneous pulmonary valve implantation should be pursued and is nowadays common. Maybe breathing training early after thoracic surgery can not only improve short-term outcomes [21] but also long-term lung function and exercise capacity. The significant positive correlation between training days/week and increase Δ peak$\dot{V}O_2$ underlies the importance of patients' compliance. The more often they train the better the results are. Meyer et al. [22] recently published a systematic review on home-based exercise interventions and they conclude that training compliance seems to be the major challenge. In the present study, 16 patients followed, as in their self-reported statement, which they trained seven days per week during the six months of training which is less than one-third. Four patients (7.4%,

Fig. 2) trained only once or twice a week and two more did not train anyway. These patients need to undergo further investigation to figure out what may help them to increase their compliance in home-based training or try to implement them to supervised training.

Conclusions

Children and young patients with repaired ToF benefit from a daily six-month inspiratory breathing training concerning exercise capacity and ventilatory function without any additional exercise practice. But patients need to be encouraged for frequent training. Further studies need to investigate whether the positive results of the current study of inspiratory volume training in Fallot patients compared to the less favorable results of inspiratory muscle training in Fontan patients are due to the different training modalities, or whether they are due to the different hemodynamic situation in these two patients groups.

Limitations

All patients are in regular tertiary care follow up in our institution where physical activity and leisure time sports are recommended. It may be, that the investigated group is over-represented by very motivated subjects which are possibly highly encouraged in doing sports. The increase of 0.5 ± 3.4 ml/min/kg in peak$\dot{V}O_2$ in the training group in the randomized trial seems to be few. However, it must be interpreted in comparison with the decline of -2.1 ± 4.7 ml/min/kg in the control group. And a total training effect of 2-3 ml/kg/min might indeed represent a clinically relevant treatment option, especially in those patients with an extraordinary response to the training, which still must be outlined.

Disclosures

None declared.

Funding Statement

The study was funded by an unrestricted grant from the "Stiftung KinderHerz". We declare that the results of the study are presented honestly and without fabrication, falsification, or inappropriate data manipulation according to the registered protocol. Additionally, we thank the whole team which was crucially responsible for its success. Parts of the study have been presented at the congresses CPX international 2019 and "Deutsche Gesellschaft für Pädiatrische Kardiologie und Angeborene Herzfehler e.V." 2020.

Competing interests

None declared.

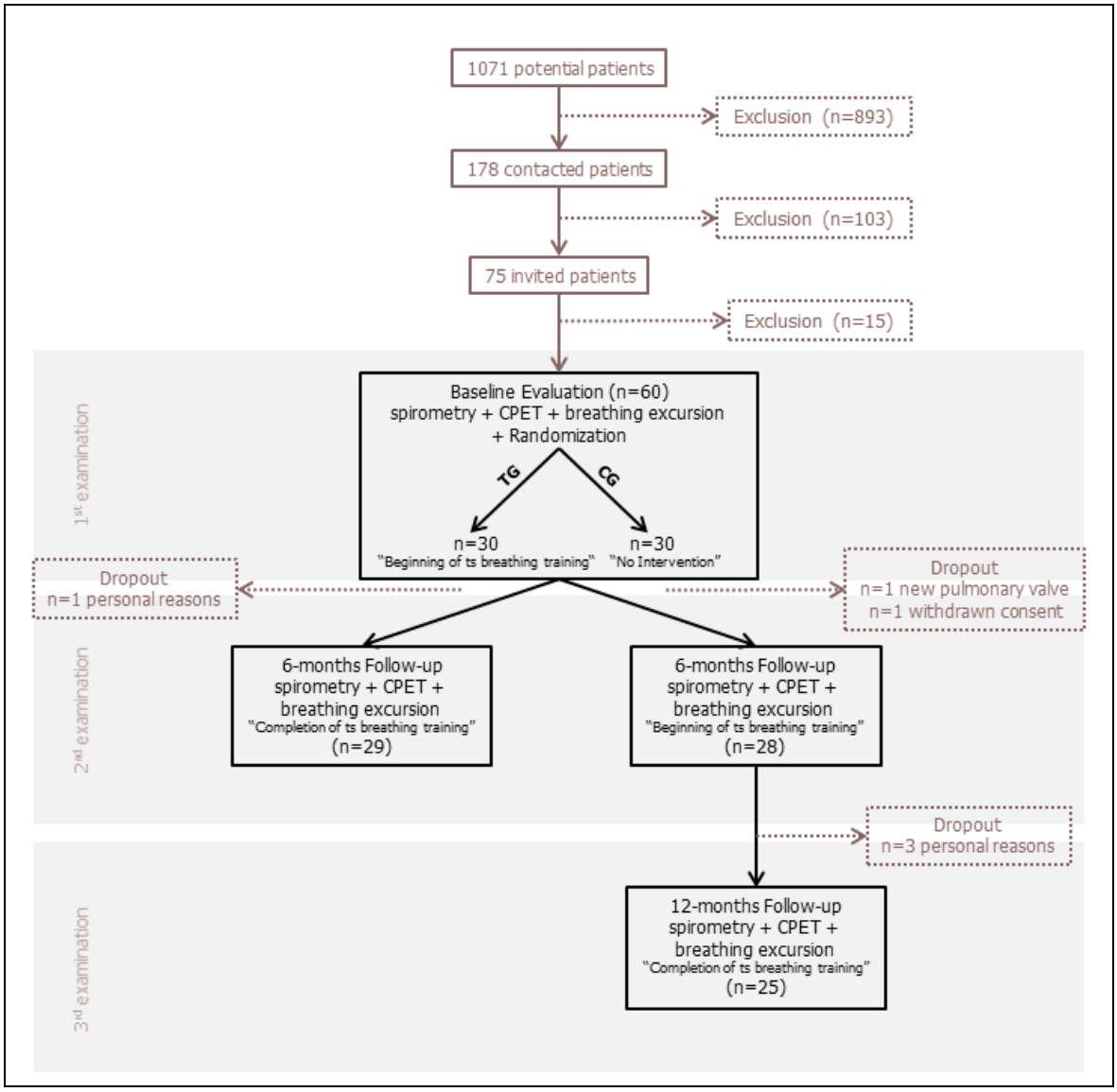
Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination of this research.

What is already known about this subject? Breathing training can influence the exercise capacity in patients with congenital heart defects.
What does this study add? Inspiratory volume-oriented breathing training in patients with repaired tetralogy of Fallot increases their exercise capacity and lung function significantly.
How might this impact on clinical practice? An inspiratory volume-oriented breathing training should be offered to patients with repaired tetralogy of Fallot to increase or at least maintain exercise capacity.

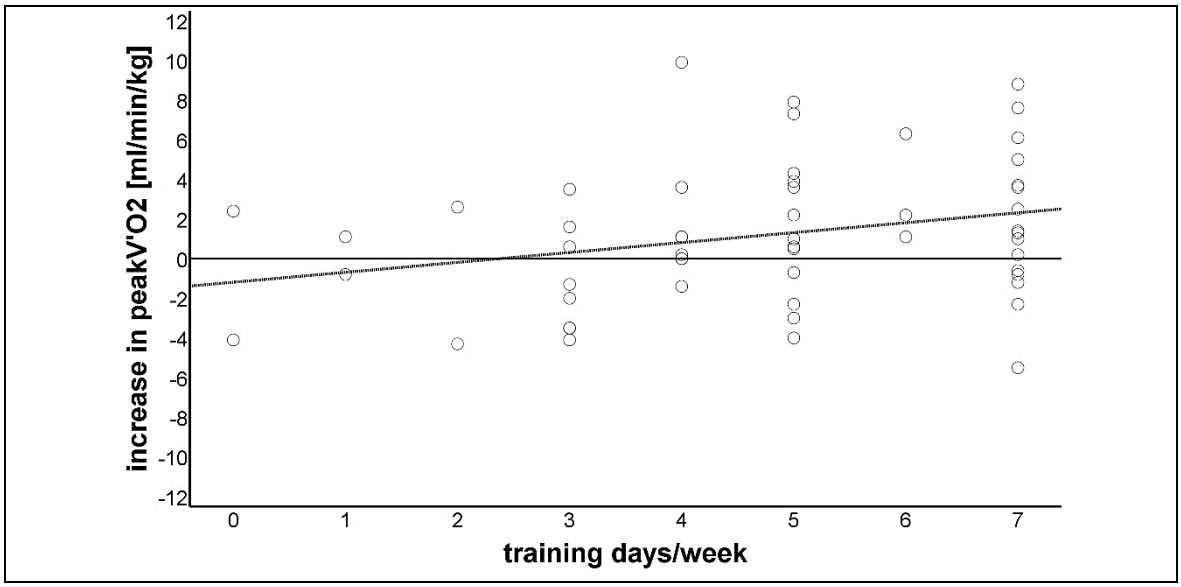
Figures

Figure 1: Study concept and patient's inclusion



n: number of patients, CPET: cardiopulmonary exercise test, TG: training group (primary training group), CG: control group (secondary training group)

Figure 2: Spearman's correlation in the increase in peakV̇O2 and training days/week for patients who have self-reported their training frequency



n=54; r=0.282; P=0.039

n: number of patients, peakV̇O2: peak oxygen uptake, ml: milliliter, min: minute, kg: kilogram; dotted line: regression line

Tables

Table 1: Patients' characteristics at inclusion

	Primary training group (n=30) mean ± SD	Secondary training group (n=30) mean ± SD
Sex (n/% female)	11/36.7	12/40.0
Age (years)	14.8 ± 5.0	15.7 ± 4.7
Height [cm]	155.4 ± 17.7	156.8 ± 16.4
Weight [kg]	50.8 ± 19.3	51.1 ± 17.0
BMI [kg/m^2]	20.1 ± 4.3	20.2 ± 4.2
Restrictive lung function (FVC<-1.64) (n/%)	13/43.3	11/36.7
Decreased exercise capacity (<80%) (n/%)	13/43.3	16/53.3
ToF (n/%)	20/66.7	23/76.7
Age at correction (months)	11.7 ± 15.0	11.7 ± 11.9
Correction (transannular; n/%)	13/43.3	17/56.7

n: number of patients, SD: standard deviation, cm: centimeter, kg: kilogram, BMI: body-mass-index, m: meter, FVC: forced vital capacity, ToF: Tetralogy of Fallot

Table 2: Results in student's T-test for independent samples in CPET

	Primary training group; n=30, mean ± SD			Secondary training group; n=30, mean ± SD			P-value*
	1st examination	2nd examination	**change**	1st examination	2nd examination	**change**	
Cardio-pulmonary-exercise test							
peak$\dot{V}O_2$ [ml/min/kg]	31.1 ± 6.5	31.6 ± 7.1	0.5 ± 3.4	31.4 ± 7.6	29.2 ± 6.5	-2.1 ± 4.7	***0.017***
peak$\dot{V}O_2$ (%pred)	80.5 ± 15.8	79.5 ± 17.4	-1.0 ± 9.0	79.2 ±16.0	75.1 ± 18.5	-4.1 ± 12.3	0.27
$\dot{V}_E/\dot{V}CO_2$ (slope)	30.2 ± 4.3	29.9 ± 4.2	-0.2 ± 1.8	29.6 ± 3.6	29.9 ± 4.4	0.3 ± 2.6	0.41
Spirometry							
FVC [L]	2.9 ± 1.0	3.0 ± 1.1	0.17 ± 0.17	3.0 ± 0.8	3.0 ± 0.8	0.06 ± 0.15	***0.010***
FVC (z-score┼)	-1.4 ± 1.2	-1.2 ± 1.5	0.2 ± 0.6	-1.6 ± 1.3	-1.6 ± 1.3	-0.0 ± 0.3	0.06
FEV1 [L]	2.5 ± 0.9	2.6 ± 0.9	0.14 ± 0.17	2.6 ± 0.7	2.6 ± 0.7	-0.02 ± 0.16	***<0.001***
FEV1 (z-score┼)	-1.4 ± 1.2	-1.2 ± 1.3	0.1 ± 0.6	-1.6 ± 1.3	-1.8 ± 1.3	-0.2 ± 0.5	***0.013***
FEV1/FVC [%]	87.3 ± 6.2	86.5 ± 5.5	-0.8 ± 5.5	86.7 ± 5.9	84.0 ± 6.3	-2.7 ± 4.2	0.13
FEV1/FVC [z-score]	0.1 ± 1.1	-0.1 ± 0.9	-0.1 ± 0.9	-0.0 ± 1.1	-0.4 ± 1.0	-0.4 ± 0.7	0.15
Breathing excursion							
difference maximum exhalation and inhalation [cm]	5.2 ± 1.6	5.6 ± 1.3	0.5 ± 1.4	5.3 ± 1.6	5.6 ± 1.9	0.4 ± 1.0	0.75

┼according to GLI 2012 references[15]; *significant with P<0.05 in student's t-test for dependent samples with raw-data; n: number of patients, SD: standard deviation, peak$\dot{V}O_2$: peak oxygen uptake, ml: milliliter, min: minute, kg: kilogram, %pred: percentage of the predicted value, cm: centimeter, $\dot{V}_E/\dot{V}CO_2$: needed liters to exhale of 1 liter of carbon dioxide, FVC: forced vital capacity, L: liter, FEV1: forced expiratory volume in the 1st second

Table 3: Intervention study: only patients who have stated a subjective training frequency (n=54)

	Pre-Training mean ± SD	Post-Training mean ± SD	Change ± SD	P-value*
Cardio-pulmonary-exercise test				
peak$\dot{V}O_2$ [ml/min/kg]	30.0 ± 6.6	31.1 ± 7.2	1.2 ± 3.6	***0.017***
peak$\dot{V}O_2$ (%pred)	77.0 ± 16.2	78.3 ± 17.5	1.3 ± 10.1	0.332
$\dot{V}_E/\dot{V}CO_2$ (slope)$_E$	30.4 ± 4.5	30.1 ± 4.3	-032 ± 2.1	0.336
Spirometry (z-Score┼)				
FVC [L]	2.9 ± 0.9	3.0 ± 1.0	0.17 ±0.20	***<0.001***
FVC (z-score)	-1.5 ± 1.3	-1.3 ± 1.5	0.2 ± 0.5	***0.010***
FEV1 [L]	2.5 ± 0.8	2.6 ± 0.8	0.15 ±0.19	***<0.001***
FEV1 (z-score)	-1.5 ± 1.3	-1.4 ± 1.3	0.2 ± 0.6	***0.037***
FEV1/FVC [%]	85.8 ± 6.5	86.7 ± 5.5	0.1 ± 5.3	0.930
FEV1/FVC [z-score]	-0.2 ± 1.1	-0.1 ± 1.0	0.0 ± 0.9	0.910
Breathing excursion				
difference maximum exhalation and inhalation [cm]	5.2 ± 1.7	6.0 ± 1.8	0.6 ± 1.4	***0.010***

┼according to GLI 2012 references[15];*significant with P<0.05 in student's one sample T-test against zero; n: number of patients, SD: standard deviation, peak$\dot{V}O_2$: peak oxygen uptake, ml: milliliter, min: minute, kg: kilogram, %pred: percentage of the predicted value, cm: centimeter,$\dot{V}_E/\dot{V}CO_2$: needed liters to exhale of 1 liter of carbon dioxide, FVC: forced vital capacity, L: liter, FEV1: forced expiratory volume in the 1st second

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6 DISCUSSION

6.1 FUNCTIONAL OUTCOMES

EXERCISE CAPACITY

Peak $\dot{V}O_2$, is a strong predictor of mortality in healthy people[99] and patients with cardiovascular diseases.[100] A higher peak $\dot{V}O_2$ is a surrogate parameter for a significant improvement in patients' survival.[100] Therefore, a CPET is an important tool to identify patients' possible risks. Several studies already proved that patients with CHD are under the risk of a lower peak $\dot{V}O_2$ compared to peers.[101-105]

Reasons are various: in TCPC patients, only one ventricle works properly. The lung perfusion is passive and therefore, the preload is reduced.[106,107] Additionally, the increase of cardiac output during exercise fails due to the patients' anatomy and technique used for cavopulmonary connection.[108]

In patients with rToF, other reasons for limited exercise capacity may be leading. They have two ventricles and "normal" circulation. During surgery, ventricular scarring occurs due to closing the ventricular septal defect with patching and extensive incision during the correction. This often leads to a prolongation in QRS duration, which is significantly associated with patients' long-term outcomes.[109] [104,110,111]

Also, a right ventricular overload is common in these patients due to a dysfunction in the right ventricular outflow tract,[112] which may lead to changes in the left ventricle, too.[113]

Patients' exercise capacity is limited by the history of their CHD, which explains a wide range in percentage of predicted. Nevertheless, during the last decades, especially in patients with univentricular heart, this percentage increased.[102] Next to medical and surgical improvements, it occurs also probably due to nowadays fewer restrictions in daily physical activity and joining leisure[114,115] or even competitive[116] sports. Different training studies tried and try to figure out if regular training may increase functional outcomes. Duppen et al.[117] and Therrien et al.[97] focus on exercise training and its effect on peak $\dot{V}O_2$, whereas they succeeded. Gruning et al.[118] mixed exercise and breathing training and figured out, that this increases the quality of life, too in patients with pulmonary hypertension. Dua et al.[119] also focus on the quality of life as an important outcome from exercise training. Fritz et al.[120] conducted breathing training in patients with Fontan circulation. They added lung volumes and oxygen saturation as important outcomes. None of these parameters could be increased, but an improvement in oxygen saturation was seen.

However, the peak $\dot{V}O_2$ still represents one of the most proper values for predicting the probability of cardiovascular events.[121,104]

HEALTH-RELATED PHYSICAL FITNESS

Still, young children, adolescents, and young adults with complex congenital heart disease are impaired in their motor skills and their development.[122-124] The reasons for this are as varied as possible causes.

One of the reasons is the open-heart surgery most patients with complex CHD must undergo. A study group from Limperopoulos et al.[125] identified neurodevelopmental status before and after surgery or length in hypothermic circulation as predictors for later motor skills. The patients were tested in fine and gross motoric and neurological status before and twelve to 18 months after surgery. Majnemar et al.[126] concluded in their long-term follow-up study that, times of deep hypothermic circulatory arrest time or acute complications during or after surgery facilitate possible late-on impairments in motor development, as well as repetitive operations. In the present studies,[92,93] both cohorts underwent at least one open-heart surgery and were under hypothermia for a time and under cardiac arrest. Further studies support, that this has an impact on late-on developments.[127,128] Fourdain et al.[129] showed in their recently published study that early screening of motor skills is essential for further development and possible individual advancement in children in general. The first two studies in this thesis underlie that, with a mean age of 13 years, the deficits still exist and are measurable. Longitudinal studies are needed to show possible changes in children's development, particularly in complex CHD patients.

HEALTH-RELATED QUALITY OF LIFE AND ARTERIAL STIFFNESS

Health-related quality of life (HRQoL) in patients with CHD is well evaluated. But different studies show different results regarding patients' values compared to healthy controls. Mellion et al.[130] have shown, that children and adolescents with CHD present lower values in HRQoL compared to healthy controls. The same results are shown in studies from Uzrak et al.[131] in children. Van den Bosch et al.[132] shows it in adult patients with Fontan circulation. In contrast, Kwon et al.[133] have shown similar HRQoL in children with ToF after repair as well as Reiner et al.[134] (children with all kinds of CHD) and Häcker et al.[135] (children with transposition of the great arteries after anatomically surgical repair) show no difference in HRQoL compared to peers. This is in concordance with the present study[92] in TCPC patients. An important reason therefore may be the patients' sense of coherence (SOC). Müller et al.[136] figured out a positive correlation between SOC and HRQoL. Apers et al.[137] conclude

that SOC is a resource for QoL and Berg et al.[138] reason SOC as a potential benefit for a good QoL, which continues to adulthood in patients with CHD. Reiner et al.[134] add that the development in the decrease of HRQoL by age is similar to healthy controls. Overall, children with CHD are born and grow up with their disease, which may affect that they do not feel their disease as a disadvantage compared to healthy controls. Further studies are needed, also compared to other congenital diseases.

Arterial stiffness is a surrogate of cardiovascular risk. Certain threshold values have been or are being established.[139,69] In patients with CHD, an increase in arterial stiffness even may have more severe consequences since their vessels often are already affected by the CHD itself. A recently published study from Häcker et al.[88] has shown that in general, children with CHD have an increased central systolic blood pressure. They highlight that this was seen especially in patients with a left heart obstruction, TCPC, or transposition of the great arteries. Patients with rToF, as in our cohort, seem not to be affected by this.[93] This may be due to the almost unaffectedness of the aorta during surgery, which itself leads to a higher risk for worse arterial stiffness.[140]

Further studies are needed with a prospective investigation in children, adolescents, and adults with rToF to see if the arterial stiffness changes negatively in the course of life.

6.2 VOLUME-ORIENTED INSPIRATORY BREATHING TRAINING

Our working group was considering a new method of improving patients' exercise performance. Since it is sufficiently proofed that exercise training increases functional outcomes, the new study concept concentrates on breathing training without any additional exercise training. In patients with CHD, conspicuous results in lung-function tests are often associated with decreased exercise capacity.[141,101,142]

Studies have shown that patients with right heart problems successfully profit from breathing training regarding exercise capacity, but also lung volumes and quality of life.[143,118,144,145] After two studies in patients with univentricular heart,[146,120] which both unfortunately failed in increasing exercise capacity, a new training concept was developed and conducted in a randomized trial.

The study from Hock et al.[98] investigated whether a volume-oriented inspiratory breathing training without any additional exercise training increases exercise capacity, lung volumes, and breathing excursion in young patients with rToF. It is well known, that exercise-training increases exercise capacity in patients with rToF.[97,117] In patients with sickened lungs as chronic obstructive lung disease[147] or lung cancer[73] a breathing training is often used for rehabilitation – same after thoracic surgery.[148] In patients with CHD, only a few small studies investigated whether breathing training improves their exercise capacity or lung function.[77,146,79,120] It is known, that there is a positive correlation between lung function and exercise capacity.[142] The investigated cohort of patients with tetralogy of Fallot often have a restriction in the lung function pattern (FVC and FEV1).[98] With the inspiratory volume-oriented breathing training, the study population overall increased their exercise capacity, lung volumes, and breathing excursion significantly. Reasons therefore may be that the breathing training favors their alveolar ventilation. This may lead to better pulmonary perfusion and finally, reduce the right heart afterload. Though we did not prove this by echo or Magnetic Resonance Imaging data, a frequently volume-oriented inspiratory breathing training improves patients' opportunities to gain more flexibility (via inspiration, seen in breathing excursion), higher lung volumes (FVC and FEV_1), and higher values in exercise capacity (peak $\dot{V}O_2$). Still, frequent training is necessary for the highest possible effect – participants' compliance plays a great role in interventional studies, especially in training studies.[149]

7 CONCLUSIONS

This thesis first demonstrates the functional outcomes limitations in children and adolescents with TCPC and rToF. Secondly, it demonstrates that an intervention with daily inspiratory volume-oriented breathing training over six months improves peak $\dot{V}O_2$ and other functional indicators in young patients with rToF. This intervention is effective without the addition of a traditional aerobic exercise component.

The first paper demonstrated significantly decreased peak $\dot{V}O_2$ and HRPF in young TCPC patients, a rare, but the most complex CHD, compared to healthy peers. On the other hand, their HrQoL was normal. Early screening of peak $\dot{V}O_2$ and HRPF is recommended since a low HRPF can be associated with a decreased peak $\dot{V}O_2$.

The second paper duplicated these deficits in young rToF patients, the most common cyanotic CHD. Additionally, we showed that their arterial stiffness is normal. Also, in these patients, screening is recommended and investigations to increase their peak $\dot{V}O_2$ and HRPF are needed.

The third paper deals with an investigation in rToF patients. We demonstrated in a prospective randomized controlled trial, that a volume-oriented inspiratory breathing training program in rToF patients with no additional exercise training increases patients' peak $\dot{V}O_2$, lung volumes, and breathing excursion over six months. This is especially relevant for rToF patients who cannot participate in exercise training.

To conclude, this thesis demonstrated the importance of ongoing and further monitoring and investigations in young CHD patients. Assessments that show the current functional outcomes can lead to interventions that improve these and patients' quality of life. Studies are needed to identify and treat deficits or impairments in physical development. The aim should always be to help young patients with CHD become as "normal" as possible.

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9 APPENDIX

9.1 ARTICLE 1: PERMISSION OF USE FOR DISSERTATION

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Contact Information

- Email Address: jhock@gmx.net
- First Name: Julia
- Last Name: Hock

Dear Colleagues,

Hope you are doing well.

I am forwarding you the below e-mail.

Dr Julia Hock contacted us about the copyright permission to use the published original article "Functional outcome in contemporary children with total cavopulmonary connection – Health-related physical fitness, exercise capacity and health-related quality of life" for her doctoral thesis.

I would appreciate if you can look into this matter and advice Dr. Julia Hock accordingly at her e-mail address "jhock@gmx.net".

Thank you in advance for taking time on handling this matter.

Kind regards,

Mary Joy Sinal
Researcher Support

9.2 ARTICLE 2: PERMISSION OF USE FOR DISSERTATION

Re: Permission to use the published original article: archdischild-2017-314733.R2

Von: "editorial thebmj" <editorial.thebmj@bmj.com>
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> With kin regards and thank you very much,
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Statutory declaration

I assure, that I have written this dissertation at the Technical University of Munich with the title: Functional outcomes in young patients with complex congenital heart disease at the Clinic for Congenital Heart Defects and Pediatric Cardiology of the Deutsches Herzzentrum München, Clinic at the Technical University of Munich (Director: Prof. Dr. Peter Ewert) under the supervision of Prof. Dr. Renate Oberhoffer-Fritz, independently and only using the listed sources, aids, and my own experience.
I further declare that the present dissertation has not yet been submitted as part of another examination or similar. Parts of the present dissertation have been presented at national and international scientific congresses.

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