Diplomarbeit

Spiroergometry, Brain Natriuretic Peptide and Cardiac Magnetic Resonance Imaging in Adults with repaired Tetralogy of Fallot

eingereicht von

Melina Anna Winkler

zur Erlangung des akademischen Grades

Doktorin der gesamten Heilkunde
(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Kinder- und Jugendheilkunde
Klinische Abteilung für Pädiatrische Kardiologie

unter Anleitung von

Univ.-Prof. Dr. Andreas Gamillscheg
OA Dr. Gernot Grangl

Graz, im Februar 2020

EIDSTATTLICHE ERKLÄRUNG

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, im Februar 2020 Melina Anna Winkler eh.

Acknowledgements

My fascination for paediatrics was sparked during my work at the practice of Priv. Doz. Dr. Peter Fritsch and Dr. Brigitte Fritsch. Supported by their incessant enthusiasm for children's well-being, I was able to gain first professional experience.

I would like to express my deep gratitude to Univ.-Prof. Dr. Andreas Gamillscheg for his never-ending support and patience during the time I spent on working for my diploma thesis. I feel very fortunate to have been able to profit from his experience and in-depth knowledge. Furthermore, I would like to thank OA Dr. Gernot Grangl for his support whenever needed. I would also like to extend my heartful thanks to OA Dr. Sandra Gasser for giving me further insights into the fascinating, yet very challenging field of cardiopulmonary exercise testing.

Special thanks go to my friends and colleagues that rendered my university years unique. Life would have been boring if I had not met all these wonderful and extraordinary people.

Last, but by no ways least, I wholeheartedly thank my family who supported me all along the way.

Content

Abbreviations and acronyms

AI	ability index
ASD	atrial septal defect
AV	atrioventricular
BSA	body surface area
bpm	beats per minute
CHD	congenital heart disease
cardiac MR	cardiac magnetic resonance imaging
CT	computed tomography
CPX	cardiopulmonary exercise testing
DORV	double outlet right ventricle
ECG	electrocardiogram
EF	ejection fraction
EROA	effective regurgitant orifice area
FISH	fluorescent in situ hybridization
FU	follow-up
FVC	forced vital capacity
GUCH	grown-up with congenital heart disease
ICD	implantable cardioverter defibrillator
IQR	interquartile range
LA	left atrium
LPA	left pulmonary artery
LV	left ventricle/ ventricular

LVEDVi	left ventricular end-diastolic volume indexed to body surface area
LV-EF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume
MRI	magnetic resonance imaging
NRI group	group without reintervention ≥18 years
NYHA	New York Heart Association
PA	pulmonary atresia
PAP	pulmonary artery pressure
PDA	Patent Ductus Arteriosus
PM	pacemaker
PISA	proximal iso-velocity surface area
PR	pulmonary regurgitation
PRF	pulmonary regurgitation fraction
PS	pulmonary stenosis
PVR	pulmonary valve replacement
RA	right atrium, right atrial
RI group	group with reintervention ≥18 years
ROC	Receiver Operating Characteristics
rTOF	patient(s) with repaired Tetralogy of Fallot
RPA	right pulmonary artery
RV	right ventricle, right ventricular
RV Dm	right ventricular diameter
RVEDVi	right ventricular end-diastolic volume indexed to body surface area

RV-EF	right ventricular ejection fraction
RVESVi	right ventricular end-systolic volume indexed to body surface area
RVOT	right ventricular outflow tract
SD	standard deviation
TOF	Tetralogy of Fallot
TR	tricuspid valve regurgitation
VSD	ventricular septal defect

>	more than
≥	more or as much as than
<	less than
≤	less or as less as

Figures and tables

Abstract

Background: After corrective surgery of the Tetralogy of Fallot (rTOF), the most prevalent cyanotic congenital heart disease (CDH), more than 90% patients can expect to reach adulthood. During adulthood, most rTOF patients have to face complications such as pulmonary regurgitation (PR), (re)stenosis of the right ventricular outflow tract (RVOT), right and/ or left ventricular (RV, LV) dysfunction, reduced exercise capacity, arrhythmia or sudden cardiac death that may require reintervention.

Patients and Methods: In this retrospective study, 97 rTOF patients ≥18 years (f: 43% m: 57%), were assessed between 2004 – 2018 at regular intervals (clinical examination, ECG, NT-pro BNP, echocardiography, spiroergometry, cardiac MR) at the outpatient clinic for adults with CHD of the Division of Paediatric Cardiology, Medical University Graz.

Results: During follow up 38/97 (39,2%) patients underwent 53 reinterventions at a mean of 24,2±7,7 years after primary repair. In 43/53 cases RVOT reconstruction and in 10/53 cases PM/ ICD implantation was performed. After reintervention, the RV end-diastolic and end-systolic volumes (RVEDVi 160±34 vs. 104±27 ml/m^2; RVESVi 94±28 ml/m^2 vs. 59±24 ml/m^2, p<0,001), the severity of the PR (PR fraction 41±20 % vs. 8±10%, p<0,001) in cardiac MR, the echocardiographic RV diameter (48±12 mm vs. 41±7 mm, p=0,005) and the NT-pro BNP (206±186 pg/ml vs. 150±107 pg/ml, p=0,015) decreased, whereas the systolic RV function increased significantly (RV-EF 40±8% vs. 46±8%, p=0,015). Systolic LV function, QRS duration, NYHA class and parameters in spiroergometry showed no significant changes following reintervention.

At the last follow-up (26,7±8 years after corrective surgery), 83/97 (85,6%) patients were in the NYHA class I, the mean RV and LV systolic functions (RV-EF 46±8%, LV-EF 58±8%) and the RV diameter (41±7%) were normally ranged, RV volumes (RVEDVi 110±29%, RVESVi 61±24%) and the NT-pro BNP value (143±93 pg/ml) mildly increased. There was no significant difference between the two groups

except for the severity of the PR in cardiac MR, with better results in the reintervention group (PR fraction 8±10% vs. 23±17%, p=0,004).

Conclusion: More than 26 years after corrective surgery, the clinical conditions of 97 rTOF patients were excellent. Nevertheless, reintervention was performed in 40% of the patients.

Kurzfassung

Einleitung: Auch nach erfolgreicher Korrekturoperation der Fallot'schen Tetralogie (TOF), ist eine lebenslange Betreuung dieser PatientInnen (Pat) notwendig. Über 90% der Pat erreichen das Erwachsenenalter, jedoch können Komplikationen wie pulmonale Regurgitation (PR), Re-Pulmonalstenosen, rechts- und/ oder linksventrikuläre (RV, LV) Dysfunktion, verminderte körperliche Belastbarkeit, Arrhythmien, bis hin zur globalen Herzinsuffizienz und plötzlichem Herztod im weiteren Verlauf auftreten, die eventuell eine Reintervention (RI) erfordern.

PatientInnen und Methoden: Eingeschlossen wurden retrospektiv alle TOF-Pat ≥18 Jahre (n=97, m: 57%, w: 43%), welche an der Ambulanz für Erwachsene mit angeborenem Herzfehler der Univ. Klinik für Kinder- und Jugendheilkunde/ Klin. Abteilung für Pädiatrische Kardiologie Graz mittels klinischer Kontrolle und mit EKG, Echokardiographie, NT-pro BNP, kardialer Magnetresonanztomographie (cardiac MR) und Spiroergometrie im Zeitraum von 2004 - 2018 betreut wurden.

Ergebnisse: Bei 38/97 Pat (39,2%) erfolgten im Mittel 24,2±7,7 Jahre nach Korrekturoperation insgesamt 53 RI, in 43/53 Fällen (81%) eine RVOT Rekonstruktionen bzw. in 10 Fällen eine Schrittmacher-/ ICD Implantation. Nach der RI verminderten sich das RV enddiastolische und endsystolische Volumen (RVEDVi 160±34 ml/m^2 vs. 104±27 ml/m^2; RVESVi 94±28 ml/m^2 vs. 59±24 ml/m^2, p<0,001), die PR-Fraktion (PRF 41±20 % vs. 8±10 %, p<0,001) im cardiac MR, der echokardiographische RV Durchmesser (48±12 mm vs. 41±7 mm, p=0,005) und das NT-pro BNP (206±186 pg/ml vs. 150±107 pg/ml, p=0,015) signifikant. Zudem verbesserte sich die RV Ejektionsfraktion (EF) signifikant nach RI (RV-EF 40±8 % vs. 46±8 %, p=0,015). Kein signifikanter Unterschied nach RI war in der LV-EF, dem NYHA Status, der QRS Länge und den Parametern der

Spiroergometrie feststellbar. Beim letzten Follow-up (26,7±8 Jahre nach Korrekturoperation), befanden sich 83/97 (85,6%) Pat im NYHA Status I, die RV- (46±8 %), und LV-EF (58±8 %) sowie der RV Durchmesser (41±7 mm) waren im Schnitt im Normbereich, die RV Volumina (RVEDVi 110±29 ml/m^2, RVESVi 61±24 ml/m^2) sowie das NT-pro BNP (143 ±93 pg/ml) leicht erhöht. Außer einer höhergradigen PR in den Pat ohne RI (PR-Fraktion 23±17 % vs. 8±10 %, p=0,004 im cardiac MR) zeigte sich beim letzten Follow-up kein signifikanter Unterschied zu den RI-Pat.

Zusammenfassung: Der überwiegende Teil der TOF-Pat zeigt 26 Jahre nach Korrekturoperation ein äußerst zufriedenstellendes Ergebnis. Im Langzeitverlauf fand bei 40% der TOF-Pat eine Reintervention statt.

1. Introduction

In about 8 out of 1000 infants, a defect in the structure of the heart and great thoracic vessels is present at birth. By this, congenital heart disease (CHD) is the most common congenital malformation and contributes significantly to child morbidity and mortality. (1–3)

Over the past decades many innovative advances in paediatric cardiac surgery have rendered it possible that patients with CHD have an increased life expectancy, leading to significant demographic changes in the CHD patient population. (4–7) Today, the growing population of grown-ups with CHD (GUCH) comprises 1.2 million in Europe and largely exceeds the number of paediatric cases. (4,8–10) Hence, the therapeutic focus has shifted more and more to the management of grown-ups. (11,12) Most GUCH patients continue to suffer from residual problems and require subsequent reinterventions. But not only functional or haemodynamic problems need to be addressed, questions about the quality of work life, leisure activities as well as regarding contraception and pregnancy need to be answered and require specialized knowledge of the underlying disease. (13,14) Following the need of adequate treatment, specialised GUCH care centres have been established all around the world and brought about a new era of specialized cardiovascular care. To ensure comprehensive therapy, all GUCH patients should be checked at regular intervals to specialized GUCH centres. (13,15–19)

In the constant struggle to ensure the best support for GUCH patients, the importance of long-term observation becomes obvious.

Within the framework of this retrospective study, the clinical condition and need of reintervention in long-term follow-up (FU) of adult patients with repaired Tetralogy of Fallot (TOF) at the GUCH outpatient clinic of the Division of Paediatric Cardiology/ Department of Paediatrics and Adolescent Medicine, Medical University Graz was investigated.

2. The Tetralogy of Fallot

TOF is accounting for approximately 10% of all CHD cases. (20) Thus, TOF represents the most prevalent form of cyanotic CHD, meaning that one out of 3,600 infants per year is born with this complex cardiac malformation in Europe, with males and females being affected equally. (6,21,22)

2.1. Cardiac embryogenesis

Despite intense research on cardiac development, the exact pathways leading to TOF are still not fully understood. To render possible the seemingly simple function of pumping blood through the system, cardiac embryogenesis relies on numerous critical and time-sensitive steps, all of which must take place in the correct order to prevent structural and functional abnormalities. Understanding the pathways and mechanisms of cardiac embryogenesis may enable new strategies for preventing cardiac malformations such as molecular therapies or foetal cardiac interventions in future. (23–26)

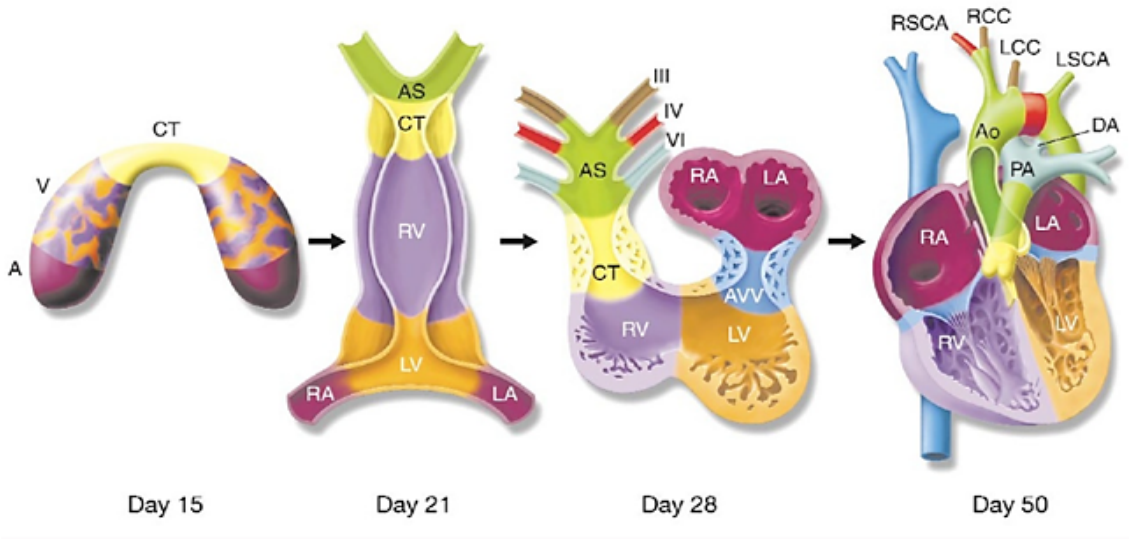

Figure 1: Cardiac embryogenesis of the human heart: The colour coding shows morphologically related regions from a ventral view. Abbreviations: A (atrium), V (ventricle), AS (aortic sac), CT (conotruncal segment), RV (right ventricle), LV (left ventricle), RA (right atrium), LA (left atrium), III, IV, VI (symmetrical aortic arch arteries), AVV (atrioventricular valve), Ao (aorta), DA (ductus arteriosus), PA (pulmonary artery), RCC (right common carotid), LCC (left common carotid), RSCA (right subclavian artery), LSCA (left subclavian artery). From: *Srivastava D et al.: A genetic blueprint for cardiac development. Nature. 2000 Sep;407(6801):221–6.*

The heart is one of the first organs to evolve and perform in the embryo. The first identifiable cardiac progenitor cells derive from three different cell lines: The cardiogenic mesoderm cells, the proepicardium, and cells from the cardiac neural crest. (24) The cardiac mesoderm cells form the so-called first and second heart field by migrating from the primitive streak to both sides of the embryo's central axis. On day 18 of gestation they organise into two endocardial tubes. The paired endocardial tubes merge and grow to form one primitive heart tube that begins to contract and beat blood as early as on day 22. Thereby, the heart is the first functional organ of the fetal organism. Only a few days later, first fetal heart tones are perceptible in ultrasound. (23,24)

Cardiac looping: To ensure sufficient blood flow to the rapidly evolving embryo, the endocardial tube has to grow and expand. The first heart field provides precursor cells for the left ventricle (LV), whilst cells of the second heard field form the atria and right ventricle (RV). Precursor cells of the epicardium and the neural crest continue their migration into the region of the heart tube. Around day 23, the endocardial tube starts to bend and loop, reaching a more midline position. This so-called "cardiac looping" is essential for the evolution of the four-chambered-heart to allow the correct location of its inflow and outflow connections. But looping not only brings the future LV more leftward and, by this means, the future RV more rightward, it also ensures a connection between the LV and the sinus venosus as well as between the RV and the truncus arteriosus (future aorta and pulmonary artery). (23,27)

In the fifth gestational week looping is completed and **cardiac septation** is the next step in the cardiac morphogenesis. At this point, the exterior appearance resembles already a mature heart, but from the inside it still looks like a single tube. During the septation of the atria, the septum primum and secundum grow together, separating the AV canal into the right and left atrium. However, a little orifice remains open – the foramen ovale allows foetal blood to pass from the inferior vena cava to the left atrium. In the meantime, the septation of the ventricles takes place as well. The primitive ventricle (future LV) merges with the bulboventricular septum and both give rise to the interventricular septum. Ventricular septum defects (VSDs) can happen at any stage of the development of the interventricular septum. The septum of the outlet segment (the bulbus cordis)

evolves from ridges of the cardiac jelly (an extracellular matrix secreted by the myocardium). The outlet septum connects the pulmonary artery to the RV and the aorta to the LV. Any deviation in cell growth requires that the smooth muscles of the outlet septum have to bridge a longer distance leading to a separation of the tricuspid and pulmonary valves. (24–26)

Defects in this phase of cardiogenesis cause conotruncal and aortic arch defects such as TOF. So far, some genes have been identified for being involved in valve formation, such as Tbx1 (associated with the Di George syndrome) and Ptpn11 (Noonan syndrome). (20,28) By day 50, the cardiac embryogenesis is completed, and the heart has grown into its mature form. (23,29)

2.2. Aetiology

Tracing back cardiac malformations to their precise aetiology is difficult. Less than 20% of CHD can be directly linked to a specific mutation (either chromosomal or single-gene) that is responsible for intervening in cardiac embryogenesis and leading to an expressed malformation. (20,26) In other words, there are numerous ways of disrupting the heart development. CHD can originate from an inherited gene mutation or an acquired de-novo somatic gene mutation during embryogenesis. Additionally, recent studies increasingly recognize epigenetics as an important factor for a cardiac malformation. An estimated 80% of the genetic triggered cases occur as sporadic events, but the risk of having a CHD increases by a factor of three in case siblings have been affected already. (22,26,30–32)

Although the aetiology of TOF remains undefined in most cases, recent research confirms that chromosomal disorders can be found in over 25% of the patients. Trisomy 13, 18 and 21, as well as 22q11.2 microdeletions and other less common chromosomal abnormalities causing velocardiofacial syndromes like the Noonan-, Alagille-, and the Di George-Syndrome are associated with TOF as well. (20,33–35)

In about 20% of the TOF patients with pulmonary stenosis (PS) and 40% with pulmonary atresia (PA) and VSD (PA/ VSD), 22q11.2 microdeletions have been found. The mutations vary in expression but are summarized by the CATCH-22-

Syndrome, an acronym that stands for cardiac abnormalities, thymus aplasia, anomalous face, cleft palate, hypocalcaemia and 22 for being the affected chromosome. It is recommended to screen TOF patients for the chromosome 22q11.2 microdeletions since this mutation raises the risk of recurrence in offspring by up to 50%. (20,26,28,36)

Environmental disturbances have been established as another important influencing factor. (24,26,28) Environmental disruptions could be more easily controlled since they are not of genetic nature. Until now the following malignant factors jeopardizing the cardiac development have been recognized: Maternal diabetes, rubella infection, systemic lupus erythematodes, untreated maternal gestation diabetes, maternal smoking, alcohol and teratogenic medicaments like anticonvulsants and retinoid acid as well as paternal exposure to phthalates, air pollutants and pesticides. (26,28,37)

2.3. Morphology

The first description of TOF dates back to 1671 when the Danish anatomist Niels Stenson described this cardiac malformation most likely for the first time. Stenson reported the case of a 16-month-old patient called ‘the blue boy’. (38) Since then, several other anatomists and doctors have confirmed these findings. In 1888, Etienne-Louis Arthur Fallot published a series of reports in the ‘Marseille Medical Journal’, describing in detail the anatomy and the pathophysiology responsible for this defect. However, Fallot did not use the term ‘Tetralogy of Fallot’; he called the condition ‘la maladie bleue’ (French for ‘blue disease’). It was a couple of years later that ‘the blue desease’ has been named after Fallot. Maude Abbott, a pioneer in paediatric cardiology in Montreal, Canada, referred to this phenotype of cardiac malformations as ‘Tetralogy of Fallot’. (37,39,40)

TOF exhibits a broad range of morphologic characteristics, but one essential cardiac malformation is defining this complex CHD which is the anterior-superior deviation of the conal septum. Due to a malalignment during the embryonal heart development, there are four morphological features characterizing the tetralogy: The VSD, with the aortic root overriding the defect and leading to the subsequent

obstruction of the right ventricular outflow tract (RVOT), and the right ventricular (RV) hypertrophy as a response to the large VSD and RVOT obstruction. (7,41)

The anterior and leftward deviation of the outlet septum leads to a failed expansion of the subpulmonary conus and hypoplasia of the RVOT. Multiple variations of the RVOT dysplasia may occur, including the hypoplasia of the pulmonary valve annulus and the bicuspid pulmonary valve with or without dysplastic, or thickened leaflets. The RVOT obstruction causes stenosis at different levels; namely to pulmonary valve stenosis in 10% of the TOF patients, to infundibular stenosis in 50%, and in 30% of the cases a combined stenosis is diagnosed. Furthermore, the hypertrophy of muscular bands in this region aggravates the subvalvar obstruction. Subsequently the RVOT obstruction reduces the pulmonary blood flow which might cause different degrees of hypoplasia and stenosis of the main pulmonary artery and its peripheral branches. (41,42)

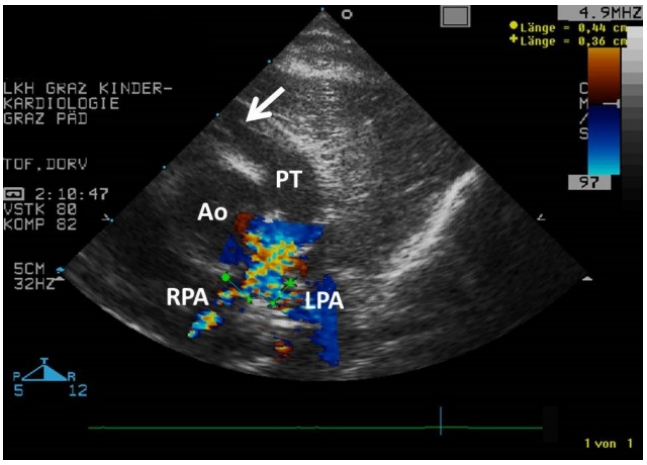

Figure 2: 2-d echocardiography of a patient with uncorrected Tetralogy of Fallot (parasternal short axis): Valvular and infundibular stenosis (←) of the right ventricular outflow tract. Abbreviations: Ao (Aorta); PT (pulmonary trunk); RPA (right pulmonary artery); LPA (left pulmonary artery). *Division of Paediatric Cardiology, Department of Children and Adolescent Medicine, Medical University Graz*

In TOF patients, the VSD is a single large malaligned subaortic defect located in the perimembranous region of the septum, and it only rarely extends to the muscular septum. The VSD is non-restrictive and leads together with the RVOT obstruction to systemic RV systolic pressure. The aortic override above the VSD varies and leads to a biventricular origin of aortic flow with an enlarged aorta and a smaller main PA. In 25% of the patients, the aortic arch is right sided. The case of

the aorta being supplied by both the LV and the RV is described as double outlet right ventricle (DORV). (7) The most severe form of TOF is a complete RVOT obstruction, a scenario referred to as PA/ VSD, occurring in approximately 10% of all TOF patients. The obstruction of the RVOT may be located at different sites: Either it is seen at the level of the pulmonary valve with well-developed pulmonary arteries or a complete obstruction of the infundibulum with only a small pulmonary artery is detected. In all these cases, there is no communication between the RV and the pulmonary arteries. With this condition, the blood flow to the lungs depends on a Patent Ductus Arteriosus (PDA) or on aorto-pulmonary collaterals. These collaterals arise from the aorta or her branches and show stenosis. In some of these cases, the native pulmonary arteries may be very small or even absent. (41)

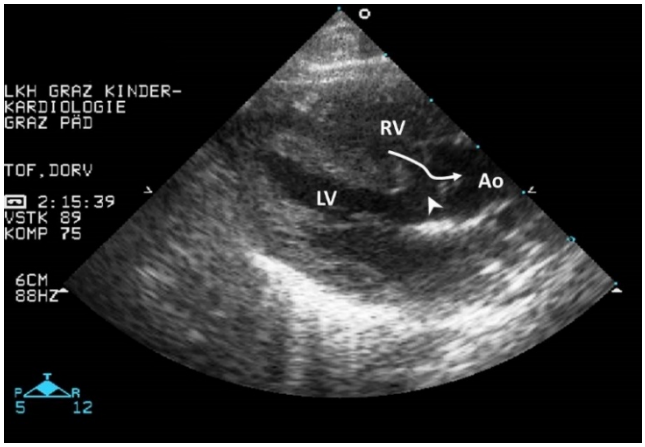

Figure 3: 2-d echocardiography of a patient with uncorrected Tetralogy of Fallot (parasternal long axis): Ventricular septum defect (◄) with aortic overriding. Abbreviations: Ao (aorta); LV (left ventricle); RV (right ventrice). *Division of Paediatric Cardiology, Department of Children and Adolescent Medicine, Medical University Graz*

2.4. Associated lesions

There are several anatomic lesions associated with TOF that affect therapy substantially. Thus, it is important to evaluate carefully the morphology of a TOF patient. Most commonly (in approximately 25% of the patients) a cardiac anomaly of the right sided aortic arch is diagnosed in association to TOF, being of particular importance when considering a palliative shunt. Multiple VSDs, a PDA, and a complete AV septal defect may be found as well, a scenario referred to as

‘pentalogy of Fallot’. Prior to surgical repair, it is important to investigate anomalies of the coronary artery branches, since in approximately 10% of the TOF patients a left anterior coronary artery arises from the right coronary sinus and crosses RVOT, thus, being significantly vulnerable during surgical intervention. (7,41)

The absent pulmonary valve syndrome is another variant of TOF worth mentioning. This syndrome is more frequently seen in patients with the Di George syndrome. (33,41) The absence of the valve leads to severe free pulmonary regurgitation (PR) and an aneurysmal dilatation of the pulmonary artery that may compress the adjacent bronchi resulting in significant air trapping.(32,41,42)

2.5. Haemodynamics

Although the pathophysiological feature of TOF is the malaligned infundibular septum resulting in a large and non-restrictive VSD, the haemodynamic consequences of TOF largely depend on the degree of RVOT obstruction. As a result of the pressure equalization through the intraventricular communication, the direction of the blood flow across the VSD is determined by the path of least resistance. If the resistance to blood flow across the obstructed RVOT is less than the resistance to flow out of the aorta into the systemic circulation, blood will naturally shunt from the left to the RV and into the pulmonary circulation. Under this condition, the left-to-right shunting predominates, and the patient will be acyanotic.

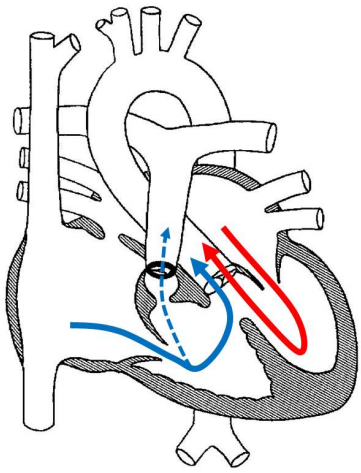

Figure 4: Schematic illustration of the haemodynamics in Tetralogy of Fallot. The blue arrow represents venous blood flow in plumonary circulation, the red arrow shows the blood flow of systemic circulation. *Division of Paediatric Cardiology, Department of Children and Adolescent Medicine, Medical University Graz*

As the RV muscles hypertrophy, the RVOT obstruction increases and the resistance to the blood flow into the pulmonary bed increases as well. If the RVOT obstruction is significant enough to augment the resistance, desaturated blood flows easier from the RV to the LV and into the systemic circulation, causing cyanosis. Pulmonary perfusion may be severely decreased depending on the severity of the RVOT obstruction.

2.6. Natural history and clinical condition

The clinical condition of TOF in infancy depends on the severity of the RVOT obstruction and the right-to-left shunt determined at birth. Most infants are born in stable haemodynamic conditions and are pink at birth (so-called ‘pink Fallots’) with oxygen saturations of about 90%. Due to the gradual increase of the RVOT obstruction, mainly caused by the infundibular stenosis, pulmonary blood flow diminishes and the right-to-left shunt via the VSD increases leading to progressive cyanosis during the first weeks or months of life. In extreme cases with significant RVOT obstruction right after birth, severe cyanosis can be already seen in the immediate new-born period. Under this condition (occurring particularly in patients with PA/ VSD) survival is dependent on the PDA or aorto-pulmonary collaterals. (7,23)

Infants with unoperated TOF may develop cyanotic attacks, so-called ‘tet spells’ during the first weeks and months of life. ‘Tet spells’ are hypercyanotic episodes that can occur spontaneously, but can be triggered by crying, feeding, waking up or pain. The infant is easily irritated, cries all the time and shows an increasing cyanosis with dyspnoea and loss of consciousness. A spasm of the infundibular muscles due to an acute increase of catecholamines causes a dynamic near-complete or complete obstruction of the RVOT and consecutively an acute decrease of the pulmonary blood flow. When the patient passes out, the infundibulum relaxes, and recovery gradually occurs. The hypercyanotic episodes can last minutes to hours, and may lead to lethargy and are lethal if untreated. (43) The gradual increase of cyanosis leads to significant limitations of activity in untreated TOF patients. This becomes obvious when toddlers try to cope with

physical exhaustion by squatting down to increase the systemic arterial resistance, and thereby driving blood back into the pulmonary circulation.

Without treatment, survival until adolescence or later is uncommon. (7,43) Untreated TOF patients suffer from the consequences of chronic cyanosis and progressive pressure overload in the RV. Polycythaemia develops due to chronic cyanosis, which causes fibrinolysis, thrombocytopenia, elevated haematocrit values and an increased risk of thromboembolism. Such patients have an increased risk of atrial and ventricular arrhythmias, tend to progressive dilation of the ascending aorta, may have a biventricular failure, systemic hypertension, cerebral thrombosis in cases of dehydration, cerebral abscess, endocarditis, and may suffer from a premature death due to heart failure as well as sudden cardiac death. Before the introduction of surgical intervention, about half of the patients with TOF died in the first few years of life. The mean life expectancy was 12 years and only 2% lived up to their 40th birthday. (41)

2.7. Diagnosis

An experienced paediatrician might suspect the diagnosis of TOF clinically; nevertheless, there are various diagnostic investigations to confirm the diagnosis. Due to advances in the field of echocardiography, the diagnosis of TOF does not necessarily require further tests such as a cardiac catheterization and/ or a computed tomography (CT)-angiography.

During a **physical examination**, unoperated children with TOF may exhibit cyanosis, digital clubbing, and may have experienced hypercyanotic episodes. Upon palpation, peripheral pulses are usually seen to be normal; only very prominent pulses can be a sign of a PDA or significant aorto-pulmonary collaterals. A palpable thrill may be observed during a very thorough inspection. Hepatomegaly in the young is very uncommon.(41)

With **auscultation**, the first heart sound is normal, whereas the second heart sound is usually a single one because of the barely audible pulmonic component. A third or fourth heart sound is very unlikely, but one may hear an early systolic click along the left sternal border that is caused by the blood flow into the ascending aorta. The characteristic systolic ejection murmur in TOF patients is mainly due to the RVOT obstruction and is described as a crescendo-decrescendo like sound with a harsh systolic ejection quality. The murmur is best auscultated along the left mid to upper sternal border. The murmur is caused by the degree of RVOT obstruction. The blood flow through the RVOT decreases as the RV hypertrophy

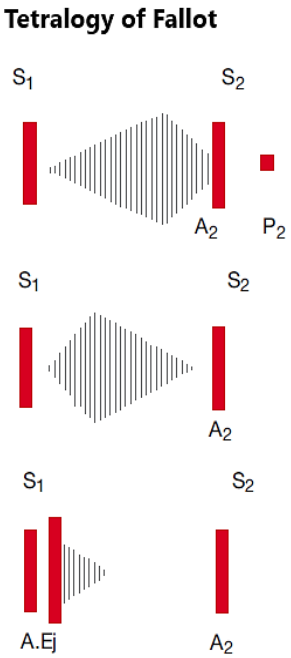

Figure 5: Auscultation of a heart with uncorrected Tetralogy of Fallot. Abbreviations: S1 (first heart sound), S2 (second heart sound), A2 (aortic component of the second heart sound), A.Ej (aortic ejection sound), P2 (pulmonic compinent). From: *Shaver JA et al. Examination of the Heart. Part IV. Auscultation of the Heart. Dallas, 1990. American Heart Association. p. 45.*

increases; thus, enforcing the right-to-left shunting across the VSD and softens the sound of the murmur. (7,44)

On the **electrocardiogram** (ECG) a sinus rhythm is typically present. Signs of right atrial (RA) enlargement, RV hypertrophy and right axis deviation may be noticed. In an ECG, systolic pressure overload is seen in prominent R waves in the right precordial leads. S-waves on the posterior leads and a qR pattern in the right sided chest leads may be observed. (7,23,45)

The classical cardiac silhouette in **chest x-ray** is a clog-shaped heart ('cœur en sabot') with an upturned apex and a concave main pulmonary artery segment secondary to RV hypertrophy. Although the heart size itself appears to be of normal size, pulmonary vascularity is reduced in most cases depending on the severity of RVOT obstruction. The aortic arch is right-sided in 25% of the TOF patients. (41)

Echocardiography provides a comprehensive and exact description of the cardiac anatomy and leads in almost every TOF patients to a decisive diagnosis and preoperative assessment. Over the past years, echocardiography has replaced invasive studies for the first diagnosis of CHD. A complete transthoracic echocardiographic assessment routinely involves a combination of M-Mode and two-dimensional imaging, continuous wave (CW) and colour Doppler flow studies. Transoesophageal echocardiography is only employed during and after surgery, monitoring the ventricular function and assessing the immediate results. (23,46) The most important features to investigate whether the patient has TOF or not are the location of the RVOT narrowing (infundibular, valvular, supravalvular, or combined), the measurement of the maximum and mean CW-Doppler gradient across the RVOT, the size of the pulmonary valve annulus, the competence of the pulmonary valve and its leaflets, the size of the main PA, its branches and their confluence. The large malaligned VSD is usually located beneath the aortic valve showing a bidirectional or right-to-left shunting in colour- and CW-Doppler echocardiography. The VSD must be evaluated in multiple views to best evaluate its full extension and to identify additional VSDs. The degree of aortic override and its connection to both the mitral and tricuspid valves should be evaluated accordingly. The aortic arch and the ascending aorta should be determined as

well. Furthermore, the coronary artery distribution and other associated abnormalities (i.e. ASD, PDA or aorto-pulmonary collaterals) should be assessed. (23,41) The haemodynamic echocardiographic assessment is particularly important for therapeutic decision making: The non-restrictive VSD leads to pressure equalization in both ventricles. Hence the degree of shunting is determined by the resistance to flow into the systemic and pulmonary circulation. By measuring the peak pressure gradient between the RV and the pulmonary artery by CW Doppler assessment of the RVOT, the systolic pulmonary artery pressure (PAP) can be estimated (systemic systolic blood pressure – peak RVOT pressure gradient = systolic PAP). In patients with only mild RVOT obstruction, the gradient across the RVOT will be low and the estimated PAP will be elevated. This group of patients will have sufficiently oxygen saturated blood, since the direction of the blood through the VSD is predominantly left-to-right ('pink Fallots'). In patients with more significant RVOT obstruction, the estimated PAP is normal whereas the CW-Doppler and colour flow mapping show a right-to-left shunting leading to the characteristic cyanosis of symptomatic TOF. (47)

The advances in echocardiography not only triggered a change in the diagnosis of TOF but have also revolutionized **prenatal diagnosis**. During a routine obstetric ultrasonography, severe cardiac malformations might be detected already but a perinatologist may also refer the patient to a specialist of foetal echocardiography in case of a reported family history of CHD (previous child, 1st degree relative), an unexplained hydrops fetalis, or a maternal condition associated with foetal cardiac pathology. Foetal echocardiography can detect TOF as early as during the 17th to 19th gestational week. Based on this diagnosis, the child's delivery and perinatal management and treatment can be optimally scheduled already. (6,7,23,48,49)

Although echocardiography can reveal most of the cardiac features, **cardiac catheterization** is needed in a few cases where echocardiographic assessment is insufficient or other abnormalities, such as aorto-pulmonary collaterals, peripheral PA stenosis or coronal artery abnormalities are suspected. Since the large VSD leads to pressure equalization on ventricular levels, haemodynamic findings of cardiac catheterization reveal mildly elevated filling pressures in both ventricles. PAP is typically normal or low. The degree of right-to-left shunting is directly measured via oxygen saturation. Additionally, cardiac interventional catherization

may be exploited for a therapeutic intervention in some TOF patients. In cases with predominant valvular PS, balloon valvuloplasty can be performed prior to surgical intervention to increase the size of the pulmonary valve annulus resulting in an increased pulmonary blood flow. (6,50)

In very rare cases, **CT angiography** is used to get further information, such as three-dimensional reconstruction of the pulmonary artery system, large vessel anomalies such as coarctation of the aorta and other anomalies. (23,41,43)

Although mainly used for observing adolescents or adults with repaired TOF (rTOF), **cardiac magnetic resonance imaging** (cardiac MR) should be listed as an additional diagnostic tool for imaging areas that are poorly accessible by echocardiography, for instance distal branch pulmonary arteries and anomalies in systemic and pulmonary venous return. (7,23)

For **differential diagnosis**, a DORV with PS, tricuspid atresia and PA with intact interventricular septum and hypoplastic RV should be considered. (21,31,51)

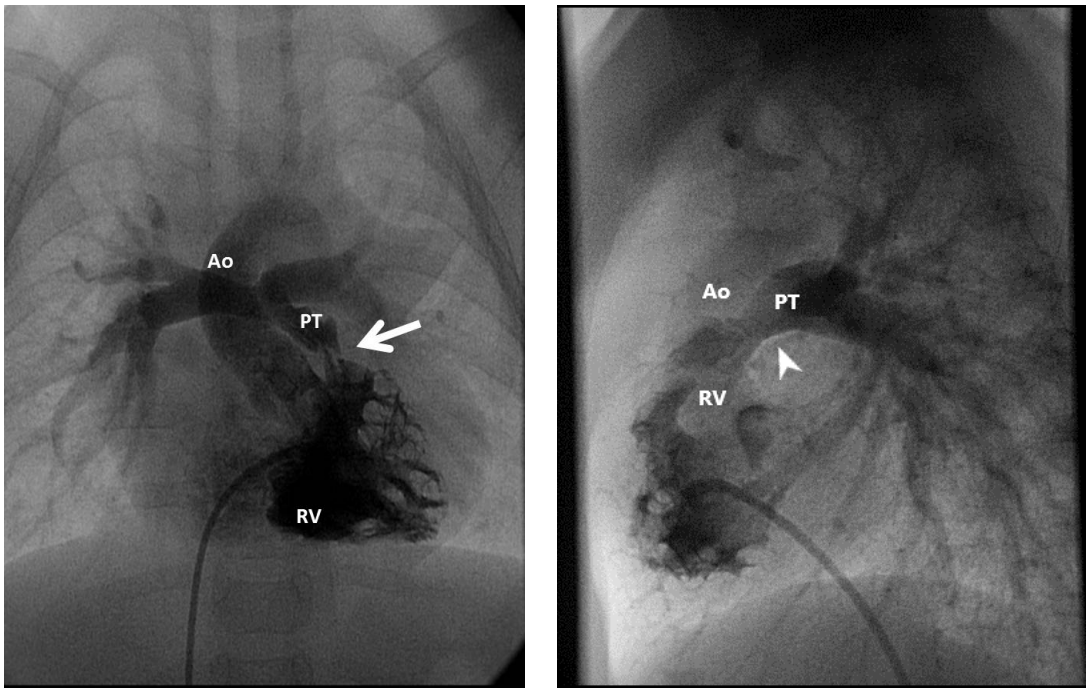

Figure 6: Right ventricular angiography (ap and lateral) of a severe RV outflow tract stenosis (←) with hypertrophied RV and reduced pulmonary perfusion. Abbreviations: Ao (Aorta), PT (pulmonary trunk), RV (right ventricle). *Division of Paediatric Cardiology, Department of Children and Adolescent Medicine, Medical University Graz*

2.8. Therapy

Nowadays, almost every child with TOF can expect to survive corrective surgery and reach adulthood. However, if we look back on the first brave surgical approaches over 70 years ago, the advances in modern medicine become apparent. Especially the history of the surgical treatment of TOF reflects the great advances in cardiac surgery of CHD over the past decades. (6,9)

The first surgical methods for treatment of TOF were palliative procedures aiming at augmenting pulmonary blood flow. In 1944, the first palliative surgery was performed by Alfred Blalock and Helen Brooke Taussig. (38) The goal was to augment the pulmonary blood flow with an end-to-side anastomosis of the subclavian artery and the ipsilateral pulmonary artery. This approach led to pulmonary hypertension and was later modified to interposing a graft (a Gore-Tex tube) between the subclavian artery and the ipsilateral pulmonary artery to ensure a controlled augmentation of the pulmonary blood flow and it became the widely applied modified Blalock-Taussig (BT) shunt. (41)

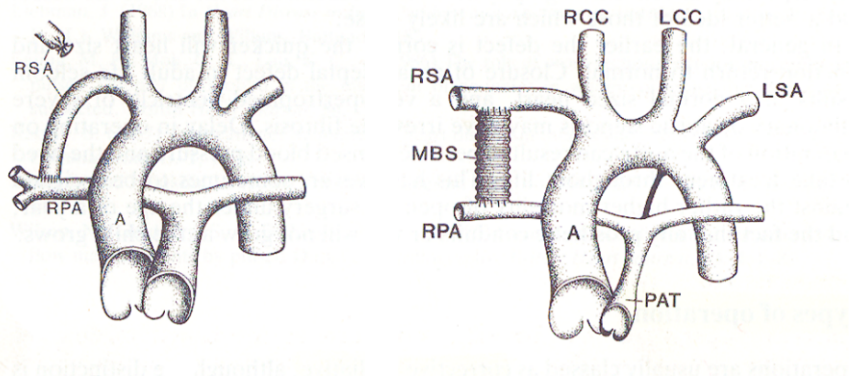

Figure 7: Classical Blalock-Taussig shunt (left) and modified Blalock-Taussig shunt (MBS, right). Abbreviations: RSA (right subclavian artery), RPA (right pulmonary artery), A (aortic arch), RCC (right common carotid), LCC (left common carotid), LSA (left sublcalvian artery), PAT (pulmonary artery trunk). From: *Jordan SC et al. Heart disease in paediatrics. 3rd ed. Butterworth & Co. 1989* (43)

Over the years, several alternative approaches and modifications to the BT-shunt were developed, such as the Waterson shunt, a side-to-side anastomosis of the ascending aorta to the main or right pulmonary artery, or the Potts shunt, a side-to-side anastomosis between the descending aorta and the left pulmonary artery.

(25) All these palliative shunts were meant to decrease cyanosis; however, they did not result in physiological cure.

It was in 1954, when Lillehei and Varco reported the first successful intracardiac corrective surgical repair of TOF. (52,53) Nowadays, the primary surgery repair is usually performed between 3 and 8 months of age. (52) There are only few cases where the infant is not yet suitable (i.e. too small or other medical reasons) for the primary surgical repair. In these rare cases, palliative bridging before the corrective surgical repair may be accomplished by implantation of a modified BT-shunt. (54) Furthermore, propranolol, a beta-blocker may be used as a prophylactic medical treatment to decrease RV hypercontractility and to prevent hypercyanotic spells. (41,50,54,55)

There are two main goals of corrective surgery: The closure of the VSD and the sufficient supply of adequate pulmonary blood flow. The VSD is closed by means of a patch to separate the systemic from the pulmonary circulation. A Persistent Foramen Ovale or secundum ASD, if present, should be addressed as well. An enlargement of the RVOT is accomplished by resecting (sub)infundibular muscle bundles and relieving PS by valvulotomy. If adequate perfusion of the pulmonary arteries cannot be achieved via a relief of the RVOT obstruction, a prosthetic graft is placed between the RVOT and the main pulmonary artery. (56)

Earlier surgical approaches (<1980) involved closure of the VSD via a large right ventriculotomy and an enlargement of the RVOT obstruction by extensive resection of the infundibular musculature in combination with an incision of the pulmonary trunk which is closed with a transannular patch. (19,37,57) Since the incision of the pulmonary valve is known to be the major cause of late pulmonary regurgitation (PR) after surgical corrective repair, surgeons aim at preserving the pulmonary valve by all means and by avoiding ventriculotomy at expenses of a modest residual stenosis. The transatrial-transpulmonary approach aims at minimizing undesired side effects such as transmural myocardial scarring and or disrupting the integrity of the pulmonary valve. (6,42,52,57–59) The promising results in infants explain why surgeons push for early surgery, since the initial procedures reduce the duration of cyanosis and allow normal growth of the RVOT and the pulmonary annulus by normalizing pulmonary blood flow. (52,57)

Another variant of TOF worth mentioning involves a different surgical approach for patients with PA/ VSD. Immediately after birth, these patients are treated with intravenous prostaglandins to maintain patency of the PDA and the pulmonary perfusion. The next step in this treatment consists of the implantation of a modified BT-shunt in the neonatal period to achieve a PDA-independent pulmonary perfusion. If there is an adequate growth of the pulmonary arteries over the following months, corrective surgery is performed between the first and the third year of life by implanting a valved conduit (i.e. homo-/ xenograft) between the RV and the pulmonary bifurcation. (56)

Perioperative complications occur in 10-12% of the surgical interventions and might be low cardiac output, cardiopulmonary arrest, arrhythmia, heart block, bleeding, diaphragm palsy, residual VSDs and PS. (60) If residual lesions such as VSDs and obstruction of the RVOT persist and are haemodynamically significant, interventional catheterization or reoperation might be needed. Patients with extreme variants of TOF such as PA/ VSD are more likely to require subsequent reintervention. A complete right bundle block after surgical repair is seen in almost every TOF patient, stemming from the incisions during the intervention. Perioperative mortality is very low and is less than 2%. (52,54)

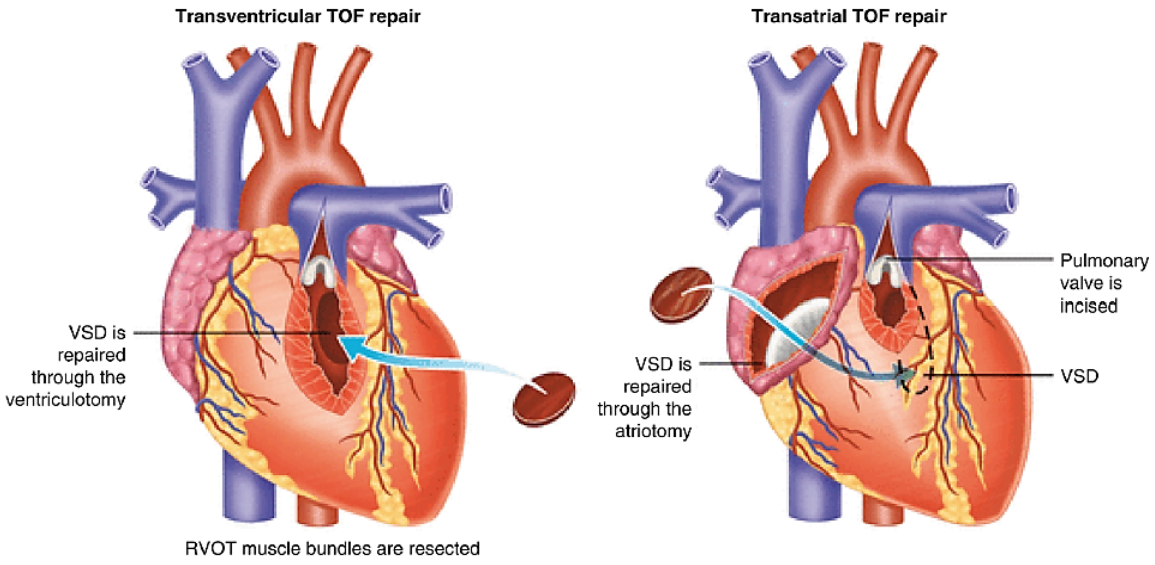

Figure 8: Transventricular (left) and transatrial-transpulmonary (right) approach to definite surgical repair of Tetralogy of Fallot (TOF). Abbreviations: VSD (ventricular septal defect), RVOT (right ventricular outflow tract obstruction). From: *van der Ven JPG, van den Bosch E, Bogers AJCC, Helbing WA. Current outcomes and treatment of tetralogy of Fallot. F1000Research. 2019 Aug 29;8:1530.*

2.9. Management of grown-ups with repaired TOF

Today, almost 90% of patients with CHD reach adult life. (14) Nevertheless, one must be aware that even an accurate and perfectly timed surgical treatment does not restore the TOF patient's heart to a complete normal condition. Despite recent advances in surgical techniques, most TOF patients continue to experience residual haemodynamic and electrophysiological abnormalities. (55,61,62) Long-term morbidity and mortality remain increased in rTOF patients when compared to their healthy age group. (9,17) Hence, these patients need lifelong expert surveillance. According to studies, GUCH patients being cared for in specialized centres have lower mortality than those managed without specialized care. (62)

On the long term, rTOF patients may develop various late postoperative complications most commonly being PR, leading to RV dilatation and tricuspid valve regurgitation (TR), residual RVOT obstruction, peripheral stenosis of pulmonary arteries, RV and LV dysfunction, arrhythmias, exercise intolerance and diffuse myocardial fibrosis. All these risk factors accelerate ventricular remodelling, worsen the clinical outcome and may ultimately lead to sustained arrhythmias, congestive heart failure, and sudden cardiac death. (6,35,55,63–67)

The surgical relief of the RVOT obstruction often involves disruption of the pulmonary valve integrity leading to significant PR in the majority of patients. (35,68) The intervention with a transannular patch plasty may induce the development of an aneurysm of the RVOT resulting in an increasing insufficiency of the pulmonary valve. Over the course of time valved xeno- or homografts placed between the RV and the pulmonary artery inevitably show a progressive degeneration by tissue calcification. This may lead to recurrent PS with or without an incompetence of the pulmonary valve. Furthermore, distortion of the pulmonary artery branches beyond the bifurcation may lead to residual or recurrent RVOT obstruction adding to the degree of insufficiency. During childhood RV volume overload is well tolerated. However, at later stages longstanding PR combined with a conduction delay caused by the nearly universal right bundle block and the dyskinetic RVOT wall leads to a progressive RV dilation and dysfunction, TR and dilation of the right atrium (RA). Chronic LV volume overload from previous palliative shunts, residual VSDs and other intracardiac shunts as well as adverse

ventricular-ventricular interaction result in progressive LV dysfunction and congestive heart failure and increases the risk of sudden cardiac death. (18,54,64,67,69,70)

Due to progressive haemodynamic problems and scarring of previous surgical interventions, atrial and ventricular tachycardia are an imminent long-term complication. The development of atrial or ventricular arrhythmia is an indication of the worsening ventricular function and TR and needs further investigation (i.e. Holter monitoring, event recording, electrophysiological testing). In adults with rTOF, cumulative incidence rates for symptomatic arrhythmias have been estimated to occur more frequently beyond 35 years of age. (19,71) Furthermore, atrial arrhythmias are significantly linked to morbidity in patients long after the corrective surgical repair of TOF and are associated with long-standing shunts, older age at corrective surgical number of reinterventions, and congestive heart failure. (42,66,71) The incidence of sudden cardiac death in rTOF is estimated to be 0,2% per year. (35,67) Hence, most sudden cardiac death events occur decades after the corrective surgery and account for a third to a half of late deaths in rTOF patients. (50,55,62,65,67,72)

Taken all complications long after corrective surgical repair of TOF into account, the need of professional life-long care and the timing of reintervention become evident.

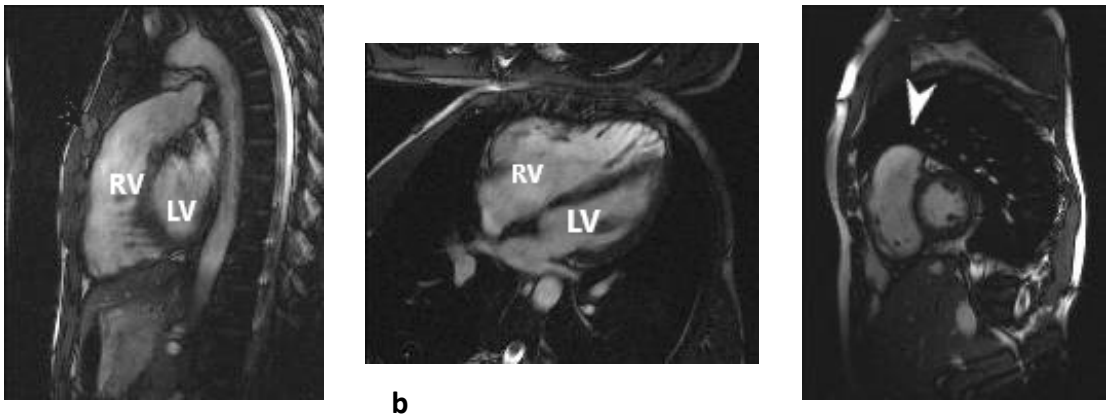

Figure 9 a-c: Cardiac MR of a patient with repaired Tetralogy of Fallot and right ventricular outflow tract aneurysma (◄) with free pulmonary regurgitation. *Division of Paediatric Radiology, Department of Radiology, Medical University Graz.*

2.9.1. Clinical condition of adult TOF patients

The clinical condition of adult rTOF patients strongly depends on the severity of anatomic malformation, its surgical correction and other environmental factors such as lifestyle. (6,73,74) Dyspnoea, palpitations and/ or chest pain, progressive exercise intolerance, as well as the history of unexplained syncopes may occur in adulthood. Signs of right heart failure such as an elevated jugular venosus pressure, peripheral oedema, hepatomegaly and ascites may arise. (41,61,75)

To evaluate the functional status of the patient (congenital or acquired), the **New York Heart Association** (NYHA) class is applied. (76) The symptoms according to the stages of heart failure are classified into the following (42):

- Class I: No symptoms and no limitation in ordinary physical activity (i.e. shortness of breath when walking or climbing stairs)
- Class II: Mild symptoms (mild shortness of breath and/ or angina) and slight limitation during ordinary activity
- Class III: Significant limitation in activity (i.e. walking short distances <100 meters) due to symptoms, but asymptomatic at rest
- Class IV: Severe limitations, symptoms are experienced even while at rest

This subjective evaluation of the patient's functional class is not only an important factor for management, but has also prognostic value in regards of morbidity and mortality. (76)

2.9.2. Auscultation

On auscultation, the most obvious symptom is that the second heart sound is heard abnormally long after the first one. A low-pitched early ending diastolic murmur indicates severe PR. RVOT obstruction is perceptible by a long and loud ejection of systolic murmur, whereas a residual VSD produces a pansystolic murmur. Aortic regurgitation could be noticed as a high-pitched diastolic murmur. (55)

2.9.3. ECG

The ECG remains an important tool in the routine evaluation of GUCH patients. A complete right bundle branch block (due to right ventriculotomy) is seen in over 98% of rTOF patients. (41,47,60) Furthermore, heart rhythm and rate and signs of RV hypertrophy can be detected. The QRS width corresponds to the degree of RV enlargement and severity of PR. A QRS prolongation (≥180 msec); especially if progressive, has reportedly shown to predict an increased risk for sustained VT and sudden cardiac death. (7,55,65)

2.9.4. NT-pro BNP

The amino-terminal pro-brain natriuretic peptide (NT-pro BNP) has evolved as a marker of RV dilation and dysfunction in TOF patients. (77–81) It is a N-terminal fragment of pro-BNP, the precursor of the biologically active BNP. The plasma concentration correlates with progressive chronic RV pressure and RV volume overload. This value is easily obtained by a blood sample from a peripheral vein and can give information about the cardiovascular reserve. (64,77,79,81,82) In the laboratory of the Medical University Graz, normal plasma levels range up to 130 pg/ml.

2.9.5. Echocardiography

As a non-invasive, widely available investigation tool with good repeatability, transthoracic echocardiography remains the go-to imaging technique to evaluate GUCH patients. (47,69,83) Since long-term complications in adults with rTOF derive mostly from the right heart, particular focus is put on the evaluation of RV parameters. (84) There are several parameters describing the morphology and function of the RV. In the context of this work, only the most significant parameters are explained in more detail.

The RV diameter (RV Dm) is used to screen for RV dilation. The RV is enlarged, if the basal RV Dm measures >41 mm in the apical 4-chamber view.(46,85) In the parasternal long axis as well as in the parasternal short axis, the dimensions of the RVOT can be assessed. In the parasternal short axis, the competence of the

pulmonary valve (trans-pulmonary artery flow and PR flow) and of the tricuspid valve (trans-tricuspid gradient and TR flow) is investigated by colour and CW-Doppler echocardiography. The RV systolic pressure is quantified by the TR flow velocity and in addition the RA pressure can be obtained based on the inferior vena cava. (85–89)

Since PR is responsible for most of the late complications in adult rTOF patients, it should be thoroughly investigated. If the ratio of the PR flow compared to the diameter of RVOT is less than a third, one speaks of a mild PR; if it is between one and two thirds, PR is moderate; and above two thirds, PR is classified as severe. Furthermore, the presence of retrograde diastolic flow in the branch of pulmonary arteries is associated with a haemodynamically significant PR. In colour Doppler, mild PR can be seen as a small flame (jet visualised in Colour flow) below the pulmonary valve; the jet of a moderate PR reaches into the RVOT, producing a diastolic flow reversal in the pulmonary artery; and the severe PR jet reaches into both branches of the pulmonary artery. The PR jet width, the RVOT diameter, and the PR jet width to RVOT diameter are quantified. (83,90)

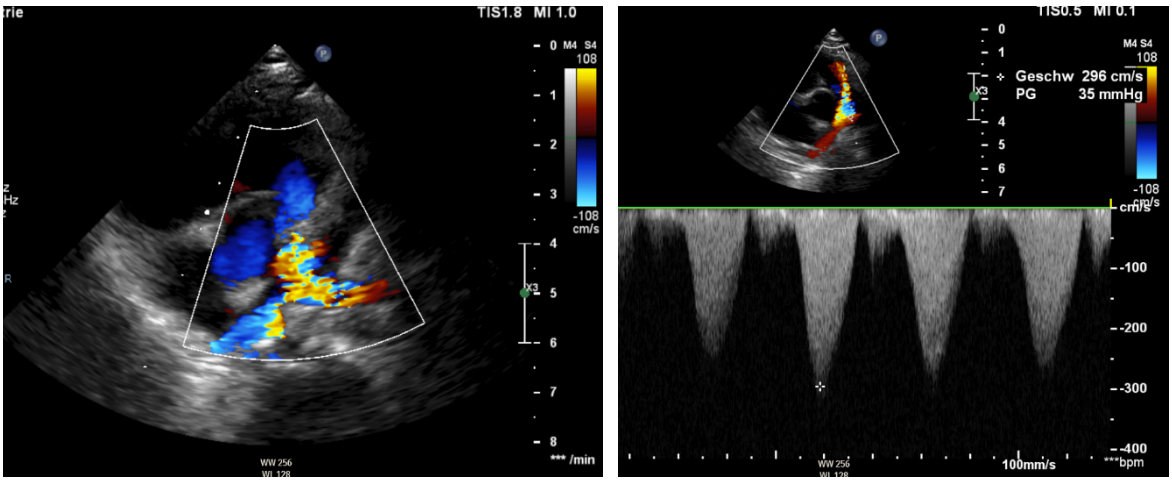

Figure 10: Colour Doppler (left) and CW-Doppler echocardiography (right) of severe right ventricular outflow tract stenosis. O*utpatient clinic for grown-ups with congenital heart disease, Division of Paediatric Cardiology, Department of Paediatrics, Medical University Graz*

The severity of PS can be classified by measuring the trans-pulmonary systolic pressure gradient with CW-Doppler echocardiography in the parasternal (or subcostal) short axis view. When compared to cardiac catheterization, this

estimation has proven reliable by itself. (46,47) Nonetheless, the presence of two stenoses (subvalvular, infundibular) or RV hypertrophy might falsely cause low pressure gradients if the cumulative pressure drop across both stenoses is not included. A peak gradient <36 mmHg is classified as mild, between 36 - 64 mmHg as moderate and >64 mmHg as severe PS. (72,86) The TR may be evaluated by the colour flow jet (retrograde TR flow) in Doppler echocardiography, the radius of the proximal iso-velocity surface area (PISA) and the effective regurgitant orifice area (EROA) or regurgitant volume. The TR can be classified in none/ mild, moderate and severe TR. (88)

Another indicator for RV dysfunction is the tricuspid annular plane systolic excursion (TAPSE), which displays the RV systolic function by measuring the excursion of the tricuspid annulus. The greater the descent of the tricuspid annular plane, the better the RV systolic function. TAPSE gained importance in the screening of adults with right-sided heart disease. Values <17 mm indicate reduced RV function. (85) However, TAPSE is load- and angle-dependent; and due to ventricular-ventricular interaction also influenced by the LV systolic performance. Thus, TAPSE should not be overestimated in its predictive value of RV dysfunction. (46,69,83)

The LV systolic function is routinely assessed to predict the global condition of the patient’s heart. A LV EF value <52% for men and <54% for women evokes an abnormal LV systolic function. (85)Although echocardiography is user-dependent and requires special expertise in the management of GUCH patients, it is a highly valuable tool to show improvements as well as the deterioration of function over time. In cases with reduced sonographic window trans-oesophageal echocardiography provides an alternative diagnostic tool. Depending on the quality of the information obtained via echocardiography, further (non-)invasive examinations may be required. (55,62,83,91)

2.9.6. Cardiac MR

Cardiac MR is the current gold standard in the evaluation of morphology and function in GUCH patients. The only limitations are related to availability, costs, and patient-related constraints (i.e. pacemaker (PM) or implantable cardioverter defibrillator (ICD) which are not suitable for MR). (47,92). Thus, cardiac MR is very important in the decision-making process of reintervention. (55,62,93)

The goals of cardiac MR assessment in rTOF patients encompass quantitative evaluation of the RV and LV volumes, of stroke volumes and of the ejection fraction (EF). The cardiac MR visualizes the RVOT anatomy including the RV dilation and dysfunction, the PS (including distal stenosis), pulmonary, aortic, and TR. (94,95)

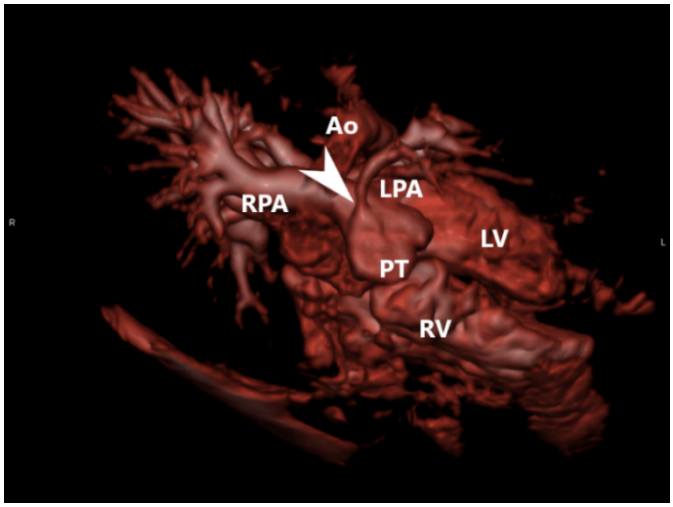

Figure 11: Cardiac MR showing severe stenosis of the left pulmonary artery (LPA ◄) . Abbreviations: Ao (aortic arch), RPA (right pulmonary artery), PT (pulmonary trunk), LV (left ventricle), RV (right ventricle). *Division of Paediatric Radiology, Department of Radiology, Medical University Graz*

Important cardiac MR parameters for the RV are the RV end-diastolic volume indexed to body surface area (BSA) (RVEDVi) and the RV end-systolic volume indexed to the BSA (RVESVi). A RVEDVi >110 ml/m^2 and a RVESVi >50 ml/m^2 indicate increased volumes. Systolic RV function is quantified by the RV-EF. A RV-EF<50% displays a reduced RV function. The degree of PR is quantified by the PR fraction (PRF). A PRF of more than 30% signals severe PR. To describe the global function of the LV, the most conclusive parameter is the LV-EF. A LV-EF <45% indicates a significantly reduced LV function. (96)

2.9.7. Spiroergometry

Cardiopulmonary exercise testing (CPX) has continuously evolved over the past decades. Once predominantly used for estimating the probability of obstructive coronary artery disease before catheterization, it now holds an important place in the management of GUCH patients. Hence, CPX is a very useful tool to objectively investigate the mechanisms and the degree of exercise intolerance, to screen for and to stratify the risk of arrhythmias, as well as to quantify the response to therapy. Furthermore, activity recommendations can be given upon request. (70,97–100) Taken the versatile application of CPX into account, it is obvious that a profound knowledge of the underlying heart defect as well as the expertise in the management of adult rTOF patients is required for its interpretation. Before testing, all patients undergo a complete medical evaluation to identify constraints and to assess the personalized risk of adverse events. (97–99,101–103)

The following variables of the CPX have reportedly been used to assess the exercise capacity of GUCH patients. They are all displayed in the 9 Wasserman charts (see Figure 13). (97,99,104,105) The aim of the test is to assess the patient's exercise capacity in a controlled setting. Hence, it is a symptom-limited test and the collaboration of the patient is vital. (102,106)

In addition to the CPX, spirometry is performed at each assessment to evaluate general changes in the lung capacity. In this study, the **forced vital capacity** (FVC; l) was assessed. To compare the corresponding percentage of the predicted value of FVC (FVC pred) is indicated.

The limit of the cardiopulmonary system is reached, if the **respiratory exchange ratio** (RER), meaning the ratio between produced carbon dioxide and used oxygen shows values greater than 1,05. Thereby it is a reliable indicator for the exercise effort of the patient. (99,102,107,108)

Indications of the termination of the exercise testing are a drop in systolic blood pressure despite an increase in workload, symptoms of the central nervous system (such as dizziness or close to a syncope), signs of poor perfusion, and arrhythmia that lessens cardiac output during exercise. (109)

CPX should not be conducted if the patient is feverish or injured, suffers under acute asthma, metabolic imbalance, severe or uncontrolled hypertension or arrhythmia, severe cardiac insufficiency and severe pulmonary hypertension (the latter is very unlikely in TOF patients). If the patient has a symptomatic aortic or mitral stenosis or a history of other, unexplained syncopes, CPX should be reconsidered. (107,108)

Maximum heart rate (bpm) is a marker of chronotropic competence of the heart. The immediate response of the cardiovascular system during dynamic exercise is the heart rate (HR). HR in sinus rhythm increases gradually with workload and oxygen demand. Factors that influence HR include medication, physical condition, sinus node function and age. For better comparability, the percentage of the predicted maximum HR (max HR pred) is used. (109)

The **peak$\dot{V}O2$** is the directly measured maximal oxygen uptake, expressed as peak oxygen uptake ($\dot{V}O_2$) normalized by sex, age, and body weight (ml/kg/min). The peak$\dot{V}O_2$ defines the limit of the cardiopulmonary system and is the most accurate variable to express aerobe capacity. (108) Possible reasons for a reduced peak$\dot{V}O_2$ are an increased left-right shunt and insufficient filling of the LV, pulmonary artery hypertension and insufficient motivation of the patient. Again, the predicted peak$\dot{V}O_2$ (peak$\dot{V}O_2$ pred) is used for better comparability.

Peak$\dot{V}O_2$ values ≤25 ml/kg/min are a sign of severe cardiopulmonary restriction. Moreover, peak$\dot{V}O_2$ is an important predictor in GUCH patients for adverse outcomes, hospitalisation, and mortality. (97,102) GUCH patients with a peak$\dot{V}O_2$ <15.5 ml/kg/min) have a predicted 2-year risk of 50% hospitalisation; whilst patients with a peak$\dot{V}O_2$ >27 ml/kg/min have a 2-year event-free survival of 97%. (98,102)

$\dot{V}E/\dot{V}CO_2$ slope or V - slope expresses the ventilatory response to the oxygen consumption divided by the carbon dioxide exhalation. (110) By this, the onset of physiological abnormalities throughout the levels of workload can be assessed. The $\dot{V}E/\dot{V}CO_2$ slope relies on two thresholds: The ventilatory thresholds VT1 and VT2. VT1 is reached when the oxygen-dependant metabolism cannot sufficiently cover the energy supply of the cells. At this point the metabolism switches to anaerobic energy production but has sufficient capacity to compensate lactate

production. VT2 marks the point at which carbon dioxide and lactate cannot be sufficiently buffered anymore and the lactate levels rise extensively.

Values between 25 - 30 are considered to be within the normal range. (111,112) The pathophysiological mechanisms leading to an elevated slope are various: Ventilation-to-perfusion mismatching, accelerated metabolic acidosis, reduced cardiac function and abnormal pulmonary haemodynamics. Another important contributor to an elevated slope is an increased stress imposed on the RV caused by an augmented PAP. A reduced slope (<20) is a sign of hypoventilation. (108)

The **maximum workload** (W/kg) is a parameter that displays the exercise capacity of a person and the general physical condition. (113) In order to compare the exercise capacity regardless of the applied protocol, the percentage of the predicted maximum workload (max workload pred) is applied. (114)

Progressive exercise intolerance is becoming increasingly more relevant as an important parameter for risk stratification of TOF patients. A peak$\dot{V}O_2$ pred ≤65% or a $\dot{V}E/\dot{V}02$ slope of ≥31, combined with a prolonged QRS duration (>180 msec) increases the risk of sustained VT or cardiac-related death by the factor of 11. (97,115)

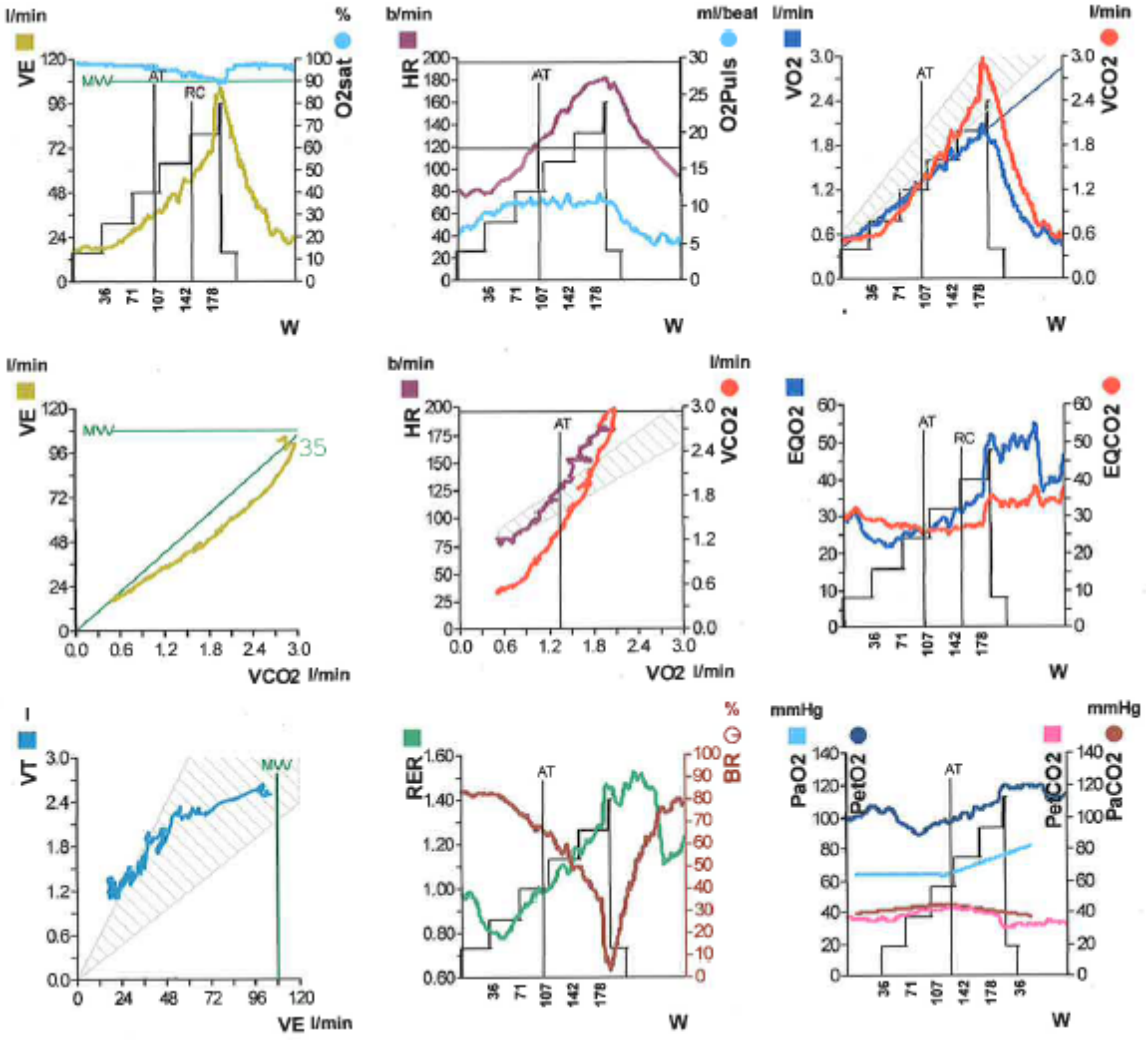

Figure 12: Cardiopulmonary exercise testing by spiroergometry of a 24 year old rTOF patient displayed in the 9 Waterman Charts. Abbreviations: VE (respiratory minute volume), W (workload in Watts), O_2sat (oxygen saturation in %), HR (heart rate in beats [b] per minute), O_2puls (oxygen uptake per heart beat in ml/beat), VO_2 (oxygen uptake in l/min), VCO_2 (exhalation of carbon dioxide in l/min) VE/VCO_2 slope (ratio of VE to VCO_2), EQO_2 (exchange quotion of O_2), $EQCO_2$ (exchange quotion of CO_2), VT (expiratory minute volume), RER (respiratory exchange ratio), paO_2 (partial oxygen saturation in atrial blood sample in mmHg), $paCO_2$ (partial carbon dioxide saturation in atrial blood sample in mmHg). *Division of Paediatric Cardiology, Department of Children and Adolescent Medicine, Medical University Graz*

2.10. Indications for reintervention

The long-term survival rate of grown-ups with rTOF is excellent with a 35-year survival rate of more than 85%. (19,116) Approximately 40% rTOF patients in their forties have undergone reintervention after corrective surgery. (7,19,41,55,59) According to the current guidelines of the European Society of Cardiology and the American College of Cardiology/ American Heart Association for the 'Management of Adults with Congenital Heart Disease', the following situations may guarantee reintervention in rTOF patients. (55,62)

In **symptomatic patients**, the decision to proceed to reintervention relies on the systolic LV and RV function. In patients with dyspnoea, chest pain, and/ or unexplained exercise intolerance, a reintervention leads to a reduction in RV size and PR and thereby to an alleviation of symptoms. (62) The following criteria are an indication for reintervention (55,62):

- severe PR with a PRF ≥30%
- PS with a RV systolic pressure ≥60 mmHg, TR velocity >3.5 m/s
- significantly decreased RV and/ or LV function (LV-EF <55%; RV-EF <45%)
- residual VSD with a shunt greater than 1,5:1

Furthermore, asymptomatic patients with worsening haemodynamic parameters may benefit from a reintervention. If one of the following conditions in **asymptomatic patients** with severe PR and/or PS is observed, reintervention should be considered (55,62):

- progressive RV dilation: RVEDVi ≥160 ml/m^2; RVESVi ≥80 ml/m^2; RVEDVi ≥2x LV end-diastolic volume indexed to BSA (LVEDVi)
- mild or moderate RV or LV dysfunction
- progressive, at least moderate TR
- residual PS (either the native RVOT or valved graft) with RV systolic pressure ≥two thirds of systemic pressure and RV hypertrophy (RV systolic pressure >80 mmHg, TR velocity >4.3 m/s)
- sustained atrial and/ or ventricular arrhythmia
- progressive decrease in objective exercise capacity
- residual VSD with significant LV volume overload

Even though TOF patients often have enlarged aortic diameters (up to 50 mm), **aortic complications** are very rare. For this reason, careful observation and risk factor management such as hypertension control has been recommended by experts. In patients with severe aortic regurgitation with signs of LV dysfunction, aortic valve replacement should be performed. (55,62)

An additional decision supporting reintervention is the dilated RV resulting in a prolonged QRS duration on the ECG. *Gatzoulis et al*. (65) reported in a multicentre study a threshold for **QRS prolongation** of ≥180 msec. Beyond this threshold, the risk of sustained VT and sudden cardiac death increases rapidly.

With advancing age and number of surgical interventions, the treatment of arrhythmia and resynchronisation therapy become more and more important in rTOF patients. The prevalence of atrial tachyarrhythmias is approximately 20% in grown-up rTOF patients, whereas ventricular arrhythmia occurs in about 15% of 35 year old rTOF patients. (71) Keeping in mind that the onset of arrhythmias might be a signal of haemodynamic decompensation accounting for most of the hospitalizations of GUCH patients; and that arrhythmias are related to an increasingly frequent cause of morbidity and mortality, careful evaluation of haemodynamics and electrophysiology is crucial. (14,55,117–119)

On the long term rTOF patients account for the largest population of GUCH patients in need of cardiac implantable electronic devices such as PM and/ or ICD. (55,62,118,119) As stated in the GUCH guidelines, patients with a history of (pre-) syncopes, and/ or heart failure with cardiac dyssynchrony limiting physical activity, benefit from a PM implantation. (55,62,117,120) A high-degree AV block is reported to be the most common indication for a PM implantation. (117,119,121) In asymptomatic patients preventive pacing is justified, if they show any of the following risk conditions: Ventricular dyssynchrony, bradycardia with a ventricular rate ≤50 bpm, ventricular pauses more than three-fold the cycle length of the underlying rhythm, complex ventricular ectopy, prolonged QTc interval, and wide QRS escape rhythm. (55,62,117)

The most recent ICD guidelines address the ICD implantation in the context of secondary prevention of sudden cardiac death. (62,67,117) If sustained ventricular tachycardia reoccurs following pulmonary valve replacement (PVR) or other

reinterventions, an implantation of an ICD for secondary prevention of sudden cardiac death is recommended.(41,55,62) In comparison to secondary prevention, primary prevention with ICDs has not been very much investigated yet. According to expert opinion, high-risk patients with sustained VT, LV dysfunction, adverse ventricular-ventricular interaction, previous palliative shunts or otherwise increased risk for sudden cardiac death, are likely to benefit from an ICD. (62,117) The risks and benefits of an ICD implantation are based on the underlying cardiac morphology, prior surgical and interventional procedures, arrhythmia and the possible need for future reintervention. Therefore, risk and benefit evaluation should be discussed in a multidisciplinary team to obtain the most objective approach possible in view of long-term effects. (118,122) Device-related complications are reported to occur in roughly 20% of patients due to lead failure, device infection, and thromboembolic events. (119,122)

2.11. Options for reintervention

There are several options for a reintervention. A joint management strategy between cardiologists and cardiac surgeons is essential to decide on the kind of technique. (41)

Open-heart surgery is chosen if reinterventions such as the relief of the RVOT obstruction, resection of a RVOT aneurysm, closure of a residual ASD or VSD, or tricuspid annuloplasty need to be performed. This is the **valve-sparing approach** to reconstruct the RVOT. In patients without advanced LV dysfunction or heart failure, RVOT reconstruction can be accomplished with mortality rates of less than <1% in specialized centres. (55) If a regurgitant or stenotic pulmonary valve needs to be replaced, PVR may be performed in open-heart surgery as well. (6,41) PVR can be conducted with a RV-to pulmonary artery valved conduit (homo-/ xenograft) or a mechanical valve.

The **mechanical valve** has the advantage of long durability. (75,123) Nonetheless, due to the thrombogenicity of materials used, high shear stress around the hinge points, and backflow jets that activate clotting-pathways, a mechanical valve requires lifelong anticoagulation therapy to avoid blood clot

formation. Thus, a mechanical valve is not the ideal choice for younger patients and women who desire to have children. (124,125)

An alternative to a mechanical valve is a **homograft.** This valved conduit comes from an aortic valve of a human donor. Since human donors are not always available, valved grafts can be made of a bovine or porcine jugular vein (**xenograft**) or are coated with a special artificial membrane. Due to the material, the valved conduits do not require anticoagulation and therefore, homo- or xenograft implantation is currently the preferred substitute of the pulmonary valve. Nonetheless, valved conduits have limited durability. In TOF patients the reported average durability of a homograft in the pulmonary position is reported to be up to 5 years after the surgical intervention. (126) After 10 years, more than 80% of the patients need a repeat reintervention or show symptomatic RV and LV dysfunction. (126–129)

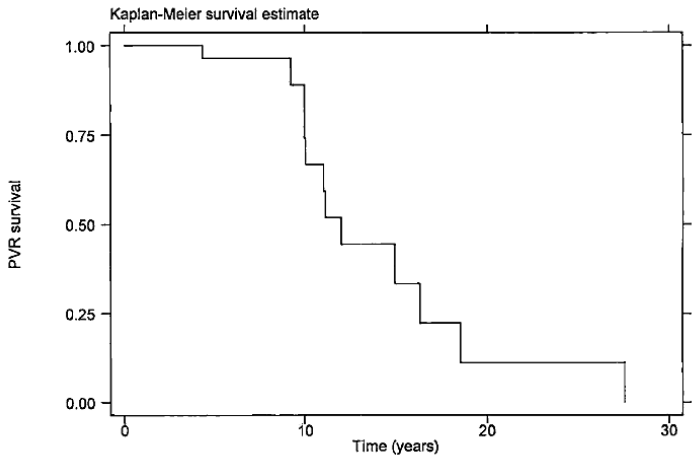

Table 1: Kaplan–Meier survival estimate of valved graft survival in pulmonary position. *From: Graham TP et al. Outcome of pulmonary valve replacements in adults after tetralogy repair: A multi-institutional study. Congenit Heart Dis. 2008;3(3):162–7.* (129)

Catheter-based intervention is chosen if a significant (distal) branch pulmonary artery stenosis needs to be dilated. Balloon angioplasty together with stent implantation are widely applied and are save procedures for the relief of distal peripheral PS. (6,130)

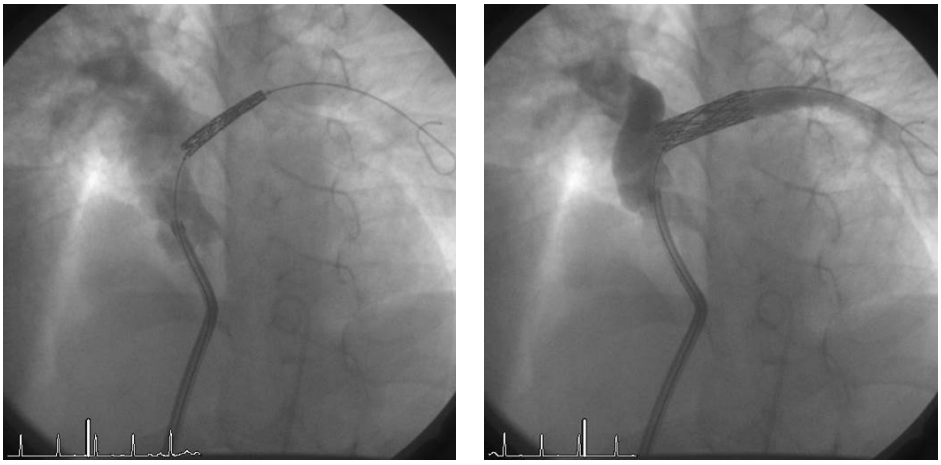

Figure 13: Transcatheter implantation of a stent in a postoperative left pulmonary artery stenois before (left) and after stent implantation (right). *Division of Paediatric Cardiology, Department of Children and Adolescent Medicine, Medical University Graz*

Transcatheter implantations of a pulmonary valve substitute becomes more and more common: **Percutaneous PVR** was developed as a minimal-invasive treatment of RVOT dysfunction. In the 1990s, the initial concept of percutaneous PVR was to extend the lifespan of a stenotic or regurgitant RV-to-pulmonary artery conduit and thereby reducing the open-heart surgeries over a patient's lifetime. (6,37) The technique and device have been improved ever since. So far, there are two types of percutaneous PVR systems available: The Medtronic Melody Transcatheter Pulmonary Valve® and the Edwards SAPIEN pulmonic Transcatheter heart Valve®. The Melody Valve® is a valved stent made from a bovine internal jugular vein affixed in a platinum stent. (131,132) Venous access is usually obtained through the femoral vein, although a jugular venous approach is also possible. After a complete haemodynamic study, a balloon test is conducted to avoid coronary compression. To reduce the risk of stent fractures at later stages, pre-stenting of the conduit is recommended. In the next step, the stented, balloon-expandable valve is brought in position and fixed in place by inflation of a balloon-in-balloon system (Figure 15). The same system but with a different type of valve is the Edwards SAPIEN pulmonic Transcatheter heart Valve®. Depending on the diameter needed for the RVOT reconstruction either a Melody Valve® or a SAPIEN Valve® is inserted. (53,61) After a failure of the primary device the balloon-expandable valve technique can also be performed as a repeat intervention (valve-in-valve technique). (133,134) Exclusion criteria for

percutaneous PVR are the risk of coronary compression by the expanded implant, a central vein occlusion or a significant obstruction, and an active infection. (93,128,133) Nonetheless, percutaneous PVR is reported to have very low perioperative mortality and shows excellent haemodynamic short- and intermediate-term results. (55,133) The risk of reintervention following percutaneous PVR ranges between 0.4% to 5.9% per patient-year. (135) By comparison to surgical PVR, higher rates of infective endocarditis have been reported. According to results from the MELODY registry the risk of infective endocarditis is estimated to be 2.3% per patient-year. (136) Other reported complications were coronary artery compression (<1%), conduit rupture (<1%), and stent fracture (in about 20% without pre-stenting, in 10% with pre-stenting). (123,134,137,138)

Considering that PR is the main reason for late sequalae in rTOF patients, PVR is the most common reintervention. (130) So far, no ideal substitute of the pulmonary valve exists. Thus, patients, who underwent PVR once, can assume to need further reinterventions later in their lives. If bears in mind that each surgical or interventional procedure carries the risk equal to the mortality and morbidity of the corrective surgical repair; the consequences accumulated over a lifetime of rTOF patients are significant. (55,130,139)

For patients with arrhythmias (either atrial or ventricular), **ablative therapy** can be performed either percutaneously or during reintervention. With this therapy arrhythmias such as a re-entrant ventricular tachycardia originating around the RVOT scar can be dealt with. (62)

If ablative therapy cannot restore an acceptable rhythm a **PM** or **ICD** is implanted. There is also the possibility of combined surgical procedures such as by restoring the haemodynamics, treatment of arrhythmia, and PM or ICD implantation during one surgical intervention. (14) In rTOF patients, PVR, ablation of ventricular arrhythmia and ICD implantation may reduce the risk of sudden cardiac death. (14,67)

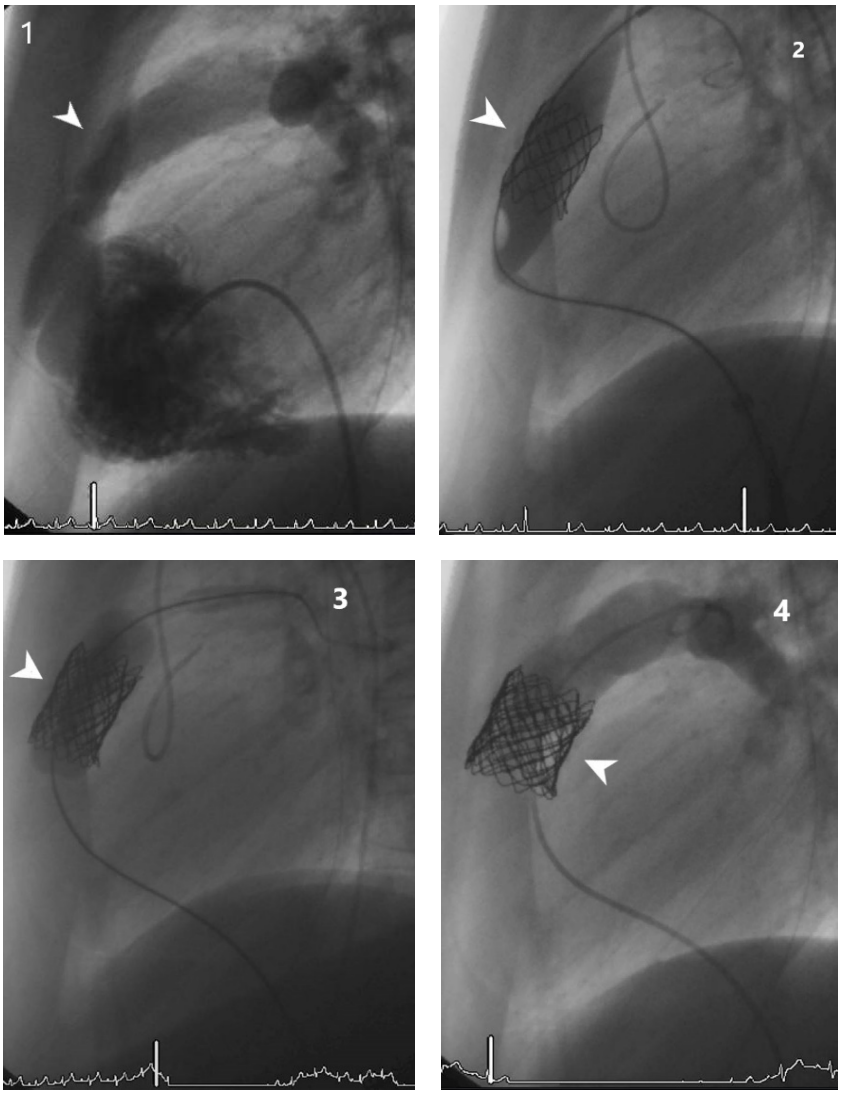

Figure 14: Right ventricular angiography and implantation of a percutaneous pulmonary valve (Melody valve®): Severe stenosis of a calcified homograft in the right ventriular outflow tract (RVOT) in a patient with repaired pulmonary atresia with VSD (1); pre-stenting of the RVOT (2); expansion of the Melody valve® in the pre-stent (3); Pulmonary angiography after valve implantation: Melody valve® with sufficent valve function (4). *Division of Paediatric Cardiology, Department of Children and Adolescent Medicine, Medical University Graz*

3. Methods and patients

This retrospective single-centre study was approved by the ethic committee of the Medical University Graz (ethic committee approval number 29-447 ex16/17).

Inclusion criteria: All TOF and PA/ VSD patients (≥18 years) were included in this study who had undergone corrective surgical repair during childhood and who were assessed at regular intervals (2004-2018) at the GUCH outpatient clinic of the Division of Paediatric Cardiology/ Department of Paediatrics and Adolescent Medicine, Medical University Graz. **Exclusion criteria**: Patients with insufficient data, or missing follow-up (FU) were excluded from the analysis.

Data were acquired with an evaluation form (enclosed in the appendix) and obtained from records of outpatients' and hospitalised patients' medical assessments in the electronic hospital information system 'Medocs' at the Department of Paediatrics and Adolescent Medicine, Medical University Graz. In this study the following examinations were evaluated: Clinical assessment, ECG, echocardiography, NT-pro BNP, cardiac MR and spiroergometry during the FU.

For the analysis the study population was divided into two groups: One group without any reintervention ≥18 years (**NRI group**), and one group with catheter-based or surgical reintervention ≥18 years (**RI group**).

At the GUCH outpatient clinic of the Division of Paediatric Cardiology/ Department of Paediatrics and Adolescent Medicine, Medical University Graz, TOF patients have usually annual routine assessments of their clinical status (including NT-pro BNP), ECG and echocardiography. Cardiac MR examination is conducted according to the patient's condition every two to three years. CPX is performed in a similar manner as the cardiac MR. The data of the different examinations were considered if they took place within a time frame of 12 months to represent the most objective picture possible of the patient's condition. To compare between the RI and NRI group data obtained within 12 months before a reintervention were used.

Standard 12-lead surface **ECG**s were analysed for the rhythm, PQ interval, and QRS duration. ECGs with PM rhythm were excluded from the comparison of conduction times. For an **echocardiographic assessment**, the Model Diagnostic Ultrasound System Philips EPIQ 5C, Software: 3.0.3 was used. **NT-pro BNP** was obtained from a venous blood sample. NT-pro BNP plasma levels >130 pg/ml were considered to be elevated. For the **cardiac MR**, the Magnetom Symphony Tim (1,5 Tesla), Magnetom Sola (1,5 Tesla), and Argus Software Numaris 4, Siemens Healthineers, Erlangen, Deutschland was used. The analysis was conducted with the cvi42 5.6.5, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada. **CPX assessment** was conducted on a cycle ergometer at the GUCH outpatient clinic. The workload was increased in levels with the goal to reach exhaustion in 8 to 12 min of the exercise according to the guidelines of the DGKS (German Society for Paediatric Cardiology and GUCH patients). (107,140) The CPX devise used was a ZAN600 Spiroergometry with ZAN 300 CO-Diffusion. For the ECG, the FLASHLIGHT ECG software and for the spirometry the ZAN100 Betterflow Spirometer/ Flowhandy was used.

The variables from the different examinations are displayed in Figure 16.

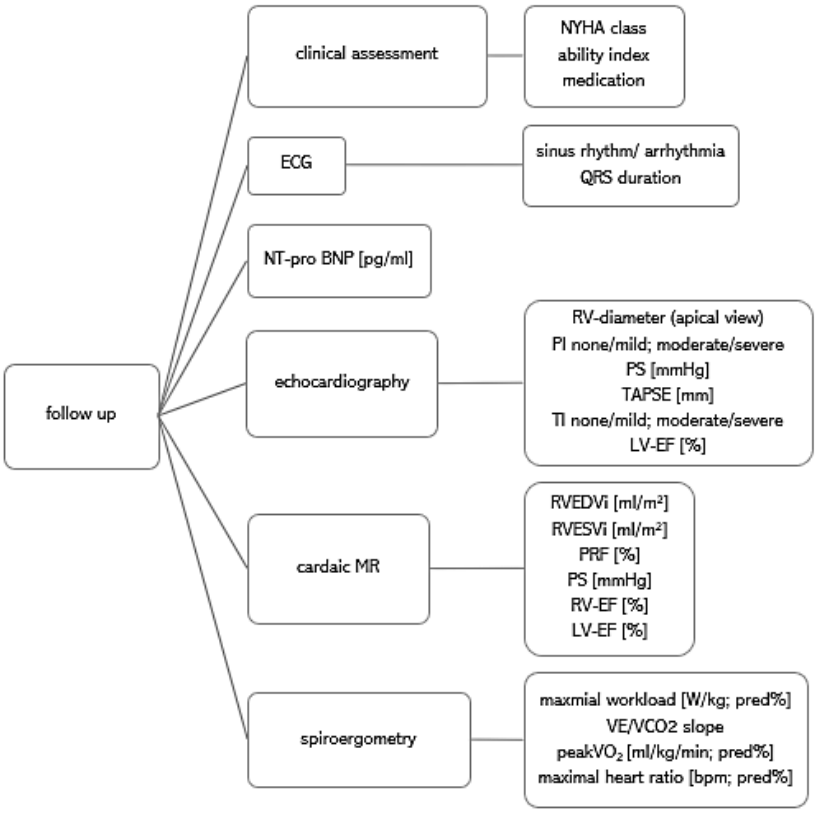

Figure 15: Data collection in patients with repaired Tetralogy of Fallot ≥18 years

4. Statistics

The acquired data were anonymised and registered in an Excel-file. The analysis was conducted with the R version 3.4.4 (The R foundation for Statistical Computing) at the Institute for Medical Informatics, Statistics and Documentation, Medical University Graz.

Continuously measured data were summarized by its mean value with ± standard deviation (SD), or its median with the interquartile range (IQR) as required. Categorical data were represented by frequencies and percentages. Variables were compared as necessary with a parametric or a non-parametric procedure by X^2, the Fisher's exact test, the Log-Rank test, the independent samples t-test, the Wilcoxon rank-sum test or the McNemar test. The univariate and multivariate analysis was conducted with the Cox hazards regression model. To evaluate sensitivity and specificity of variables the Receiver Operating Characteristics (ROC) analysis according to the Youden criteria was performed.

A p-value $p<0,05$ was considered to indicate statistical significance.

5. Results

In the first section (5.1) of this chapter the study population is described. In the subsequent section (5.2) the NRI group at their last FU and the RI group at the FU before reintervention are compared to evaluate the patient's condition that requires reintervention. In section Fehler: Verweis nicht gefunden the indications to proceed to reintervention are shown and the changes in the patients before and after the reintervention are analysed. In the last section (5.4) the clinical conditions of all patients (NRI group and RI group) at the last FU were analysed.

5.1. Characteristics of the study population

In our hospital information system, there were 127 patients with rTOF or repaired PA/ VSD at an age ≥18 years registered. Due to inconsistent data acquisition 30 patients had to be excluded. The final analysis was conducted with 88/97 (90,7%) rTOF patients and 9/97 (9,3%) patients with repaired PA/ VSD. The study population comprised 42/97 (43,3%) female and 55/97 (56,7%) male patients.

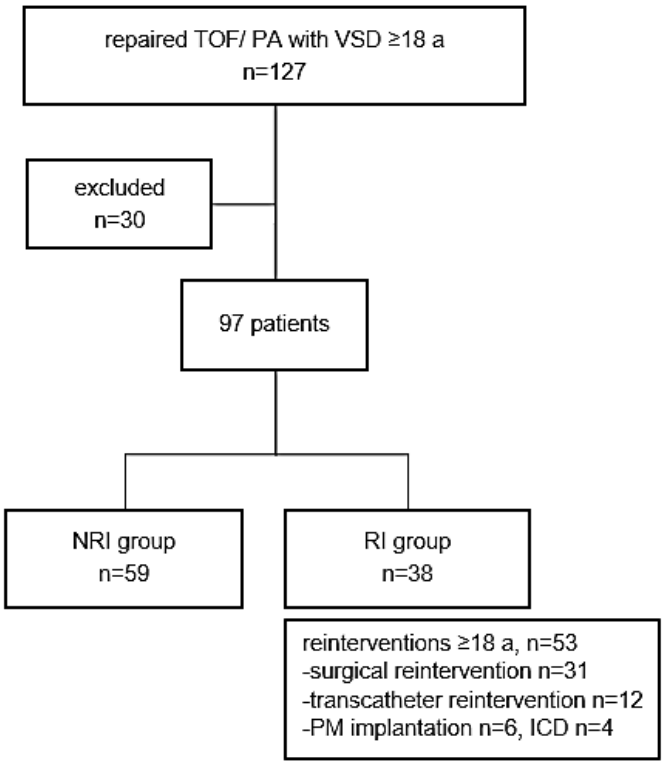

Figure 16: The study population. Abbreviations: TOF (Tetralogy of Fallot), PA (pulmonary atresia) with VSD (ventricular septum defect), FU (follow-up), a (years), NRI (no reintervention ≥18 years), RI (reintervention ≥18 years), PM (pacemaker), ICD (implantable cardioverter defibrillator)

During childhood palliative surgery before the corrective surgical repair has been performed as a modified BT-shunt in 34/97 (35,1%) patients. The mean age at the corrective surgical repair was 3,3 ±3,1 years (3 months - 14,3 years). In 47/97 (48,5%) patients a transannular patch plasty has been performed during the corrective surgical repair.

Under the age of 18 years 25/97 (25,8%) patients have already undergone 34 reinterventions. Combined procedures were performed in 9/25 (36%) patients. The indications for these reinterventions were the following: RVOT reconstruction in 15

patients, closure of residual VSD in 8 patients, homograft implantation in pulmonary position in 6 patients, balloon angioplasty of PA branch stenosis in 3 patients, percutaneous valve implantation (Melody Valve®) in 2 patients.

5.2. Comparison of the NRI and RI group

For the comparative analysis only data of reinterventions at an age ≥18 years were used. If a patient has undergone more than one reintervention, data of the most recent one was evaluated. Taken all reinterventions in a patient's adult life together, 53 reinterventions had taken place in the 38/97 (39,2%) patients (RI group). In contrast 59/97 (60,8%) patients have not undergone any reintervention ≥18 years (NRI group). To compare both groups, the time of measurement was chosen as the last FU in the NRI group and the last FU before reintervention in the RI group (see Table 2).

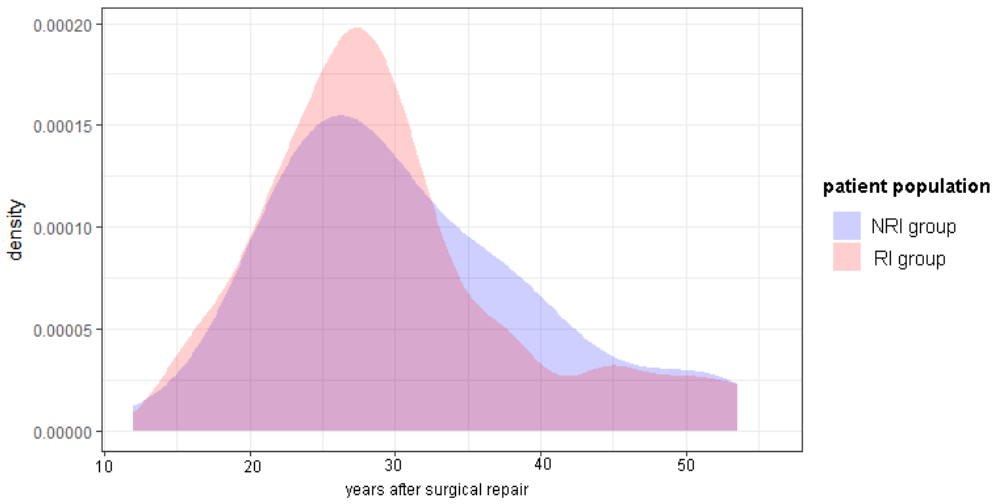

Figure 17: Time interval of follow-up (time of definive surgical repair to latest follow-up)

As shown in Figure 18 there was no statistical difference in the time of FU after the corrective surgical repair between the both groups (NRI 24,9 ±7, (7-44) vs. RI 24,2 ±7,7 (13-45) years).

In patients with transannular patch plasty during the primary corrective surgical repair a tendency for a reintervention in adult life with a hazard ratio (HR) of 1,76 and a confidence interval (CI) of 0,90 – 3,43 was found.

Patients in the RI group showed a significantly reduced systolic RV function in the cardiac MR (RV-EF 40 ±8 (20-60) % vs. 46 ±8 (20-60) %, p=0,001), a larger echocardiographic RV Dm (48 ±12 (34-87) vs. 41 ±8 (27-58) mm; p=0,007), increased RV volumes in the cardiac MR (RVEDVi 160 ±34 (106-238) vs. 114 ±29 (68-235) ml/m^2, p=0,002; RVESVi 94 ±28 (38-157) vs. 63 ±24 (33-185) ml/m^2, p=0,001), increased severity of PR in cardiac MR (PRF 40 ±20 (0-80) % vs. 23 ±17 (0-60) %, p=0,001) and in echocardiographic assessment (PR moderate/ severe in 33/38 (96,8%) vs. 36/59 (61%) patients, p=0,01).

Although severe PS was present in a few patients, echocardiographic assessment significantly revealed more often higher grades of PS in RI patients than in NRI patients (9/38 (23,7%) vs. 3/59 (5,1%), p=0,002). This significant difference, however, was not evident in cardiac MR (2/38 (5,3%) vs. 3/59 (5,1%), p>0,05).

Increased levels of NT-pro BNP were measured in the RI group (206 ±186 (20-841) vs. 103 ±78 (13-436) pg/ml, p=0,03). There was a significant correlation with the severity of PR (PRF in cardiac MR; p=0,042) and age (p=0,013).

No statistical difference between the RI and the NRI group was evident in the NYHA class (NYHA class I 27/38 (71%) vs. 52/59 (88,1%) patients). Furthermore, the LV systolic function showed no significant difference (RI 56 ±8 (40-70) vs. NRI 57 ±8 (30-80), p>0,05). Additionally, the QRS duration did not significantly differ between the two groups (RI 152 ±24 (90-200) vs. NRI 152 ±24 (90-200), p>0,05).

With the CPX assessment no statistical significance of none of the investigated parameters of any group could be discerned.

The variables used for the comparison between these both groups are displayed in Table 2.

	NRI, n=59	**before RI**, n=38	**p-value**
palliative surgery before repair	17/59 (28,8%)	17/38 (44,7%)	>0,05
mean age at repair [years]	3,4 ±3,1 (0,25-14)	3,1 ±2,8 (0,4-14,3)	>0,05
transannular patch at repair	23/59 (39%)	24/38 (63%)	>0,05
age at FU [years]	28,3 ±9,3 (18-54)	27,7 ±8,7 (18-51,4)	>0,05
time of FU [years]	24,9 ±7 (7-44)	24,2 ±7,7 (13-45)	>0,05
NYHA class I	52/59 (88,1%)	27/38 (71%)	>0,05
NYHA class II-III	7/59 (11,9%)	11/38 (29%)	
medication	21/59 (35,6%)	19/38 (50%)	>0,05
QRS duration [msec]	149 ±20 (100-180)	152 ±24 (90-200)	>0,05
NT-pro BNP [pg/ml]	103 ±78 (13-436)	206 ±186 (20-841)	**0,03**
echocardiography			
RV Dm (apical 4-ch view) [mm]	41 ±8 (27-58)	48 ±12 (34-87)	**0,007**
TAPSE [mm]	17,4 ±3 (10-25)	16,4 ±4,3 (11-25)	>0,05
PR none, mild	23/59 (39%)	3/38 (8%)	**0,01**
PR moderate, severe	36/59 (61%)	33/38 (96,8%)	
PS > 36mmHg	3/59 (5,1%)	9/38 (23,7%)	**0,002**
TI none, mild	53/59 (89,9%)	29/38 (76,3%)	>0,05
TI moderate, severe	6/59 (10,2%)	9/38 (23,7%)	
LV-EF [%]	59 ±6 (45-79)	58 ±9 (45-77)	>0,05
cardiac MR			
RVEDVi [ml/m^2]	114 ±29 (68-235)	160 ±34 (106-238)	**0,002**
RVESVi [ml/m^2]	63 ±24 (33-185)	94 ±28 (38-157)	**0,001**
RV-EF [%]	46 ±8 (20-60)	40 ±8 (20-60)	**0,001**
PRF [%]	23 ±17 (0-60)	40 ±20 (0-80)	**0,001**
PS > 36 mmHg	3/59 (5,1%)	2/38 (5,3%)	>0,05
LF-EF [%]	57 ±8 (30-80)	56 ±8 (40-70)	>0,05
spiroergometry			
maximum HR [bpm]	170 ±18 (121-194)	181 ±10 (158-193)	>0,05
max. HR pred [%]	88 ±10 (60-100)	94 ±6 (80-100)	>0,05
max. workload [W/kg]	2,3 ±0,6 (0,6-3,9)	2,2 ±0,5 (1,4-3,3)	>0,05
max. workload pred [%]	85 ±17 (50-130)	82 ±13 (60-110)	>0,05
peak$\dot{V}O_2$ [ml/kg/min]	31,4 ±9 (18,4-53,6)	29,2 ±5 (18,3-40,6)	>0,05
peak$\dot{V}O_2$ pred [%]	86 ±19 (50-140)	80 ±17 (50-100)	>0,05
$\dot{V}E/\dot{V}CO_2$ slope	25,3 ±3,3 (21-35)	27,4 ±3,8 (21-35)	>0,05
FVC [l]	4,2 ±3,3 (2,2-6,3)	3,9 ±1,4 (1,8-6,1)	>0,05
FVC pred [%]	95 ±14 (60-130)	88 ±18 (60-110)	>0,05

Table 2: The point of measurement is the last follow-up (FU) in the group without reintervention (NRI) and the FU before reintervention in the group with reintervention (RI). Abbreviations: RV (right ventricle), RV Dm (RV diameter), 4-ch (4 chamber view), TAPSE (tricuspid annular plane systolic excursion), PR (pulmonary regurgitation), PS (pulmonary stenosis), TI (tricuspid valve insufficiency), LV-EF (left ventricular ejection fraction), RVEDVi (right ventricular enddiastolic volume indexed to body surface area [BSA]), RVESVi (right ventricular endsystolic volume indexed to BSA), RV-EF (right ventricular ejection fraction), PRF (pulmonary regugritation fraction), HR (heart rate), pred (of predicted values).

5.3. Patients before and after reintervention

In 38 patients 53 reinterventions (including PM and ICD implantation) were performed at an average of 24,2 ±7,6 (13-45) years after corrective surgical repair (see Table 3).

Indications for surgical or catheter-based reintervention were the PR with a RV dilation (n=25), a relevant PS (n=7) or a combined PR and PS (n=6), a residual VSD (n=5). Indications for a PM or ICD implantation were a high-degree AV block (n=5), a symptomatic bradycardia (n=3), atrial flutter (n=1) and a symptomatic extra systoly (n= 1). In 31/53 (58,5%) reinterventions, RVOT reconstruction was performed as an open-heart procedure (homo-/ xenograft implantation n=16, mechanical valve implantation n=4, closure of VSD n=5, conservative surgical valve reconstruction n=6). Catheter-based reinterventions were performed in 12/53 (22,6%) reinterventions (Melody Valve® implantation n=8, balloon angioplasty n=4). A PM (n=6) or ICD (n=4) was implanted in 10/53 (18,9%) reinterventions. During the FU time interval 11 patients needed a second reintervention: RVOT reconstruction was conducted in 9 patients and 2 patients solely underwent a transcatheter valve implantation of a calcified homograft.

Following RVOT reconstruction (43/53 [81,1%]) there was a significant increase of the systolic RV function (RV-EF 40 ±8 (20-60) vs. 46 ±8 (30-70) %, p=0,015) and a significant reduction of the RV volumes (RVEDVi 160 ±34 (106-238) vs. 104 ±27 (71-194) ml/m^2, p<0,001; RVESVi 94 ±28 (38-157) vs. 59 ±24 (33-130) ml/m^2, p<0,001) in the cardiac MR. After reintervention the pulmonal valve showed significantly lower grades of the PR in the cardiac MR (PRF 41 ±20 (0-80) vs. 8 ±10 (0-40) %, p<0,001) and in echocardiography (PR none/ mild in 5/38 (13,2%) vs. 30/38 (79) % patients, p<0,001). The echocardiographic RV Dm (48 ±12 (34-87) vs. 41 ±7 (29-58), p=0,005) was significantly reduced. In those patients with severe PS undergoing a reintervention the PS was significantly reduced afterwards in echocardiography (9/38 (23,7%) vs. 0/38 (0%), p=0,02).

NT-pro-BNP levels significantly decreased after the RVOT reconstruction (206 ±186 (20-841) vs. 150 ±107 (20-412) pg/ml, p=0,015). In the NYHA class, QRS duration, TAPSE, LV-EF, medication, and CPX assessment, there were no significant changes before and after the reintervention (see Table 3).

	before RI, n=38	**after RI**, n=38	**p-value**
age at FU [years]	27,3 ±8,6 (18-51)	32,5 ±8,2 (20-57)	p<0,001
time of FU [years]	24,2 ±7,7 (13-45)	29,4 ±7 (15-52)	p<0,001
NYHA class I-II	27/38 (71%)	31/38 (81,6%)	>0,05
NYHA class III-IV	11/38 (29%)	7/38 (18,4%)	
medication	19/38 (50%)	26/38 (68,4)	>0,05
QRS duration [msec]	152 ±24 (90-200)	153 ±25 (90-206)	>0,05
NT-pro BNP [pg/ml]	206 ±186 (20-841)	150 ±107 (20-412)	**0,015**
echocardiography			
RV Dm (apical 4-ch view) [mm]	48 ±12 (34-87)	41 ±7 (29-58)	**0,005**
TAPSE [mm]	16,4 ±4,3 (11-25)	15,5 ±3 (11-22)	>0,05
PR none, mild	5/38 (13,2%)	30/38 (79) %	**<0,001**
PR moderate, severe	33/38 (86,8%)	8/38 (21) %	
PS >36mmHg	9/38 (23,7%)	0/38 (0%)	**0,02**
TI none, mild	29/38 (76,3%)	33/38 (86,8%)	>0,05
TI moderate, severe	9/38 (23,7%)	5/38 (13,2%)	
LV-EF [%]	59 ±9 (45-77)	60 ±8 (45-74)	>0,05
cardiac MR			
RVEDVi [ml/m^2]	160 ±34 (106-238)	104 ±27 (71-194)	**<0,001**
RVESVi [ml/m^2]	94 ±28 (38-157)	59 ±24 (33-130)	**<0,001**
RV-EF [%]	40 ±8 (20-60)	46 ±8 (30-70)	**0,015**
PRF [%]	41 ±20 (0-80)	8 ±10 (0-40)	**<0,001**
PS >36 mmHg	3/38 (5,3%)	0/38 (0%)	>0,05
LF-EF [%]	56 ±8 (40-70)	59 ±7 (40-80)	>0,05
spiroergometry			
max. HR [bpm]	181 ±10 (158-193)	167 ±16 (130-187)	>0,05
max. HR pred	94 ±6 (80-100)	90 ±10 (70-100)	>0,05
max. workload [W/kg]	2,2 ±0,5 (1,4-3,3)	2,2 ±0,4 (1,6-3,1)	>0,05
max. workload pred [%]	82 ±13 (60-110)	86 ±15 (70-120)	>0,05
peak$\dot{V}O_2$ [ml/kg/min]	29,2 ±5 (18,3-40,6)	28,2 ±7 (18,5-46)	>0,05
peak$\dot{V}O_2$ pred [%]	80 ±17 (50-100)	84 ±19 (50-150)	>0,05
$\dot{V}E/\dot{V}CO_2$ slope	27,4 ±3,8 (21-35)	25,1 ±3,1 (18-33)	>0,05
FVC [l]	3,9 ±1,4 (1,8-6,1)	3,9 ±1,3 (2-6,1)	>0,05
FVC pred [%]	88 ±18 (60-110)	88 ±15 (60-110)	>0,05

Table 3: Patients before (before RI) and after reintervention (after RI) ≥18 years. Point of measurement: last follow-up (FU) before RI; latest FU after RI. Abbreviations: RV (right ventricle), RV Dm (RV diameter), 4-ch (4 chamber view), TAPSE (tricuspid annular plane systolic excursion), PR (pulmonary regurgitation), PS (pulmonary stenosis), TI (tricuspid valve insufficiency), LV-EF (left ventricular ejection fraction), RVEDVi (right ventricular enddiastolic volume indexed to body surface area [BSA]), RVESVi (right ventricular endsystolic volume indexed to BSA), RV-EF (right ventricular ejection fraction), PRF (pulmonary regugritation fraction), HR (heart rate), pred (of predicted values).

To investigate the decision-making whether to proceed to reintervention or not, the variables were evaluated in a ROC analysis. From all the investigated variables, the following values of the cardiac MR were ranked as highly decisive: RVEDVi (AUC 0.86, 95% CI, 0.78 – 0.94, p=0.001), RVESVi (AUC 0.83, 95% CI, 0.74 – 0.93, p=0.001) and RRF (AUC 0.75, 95% CI, 0.64 – 0.86, p=0.03). QRS duration and CPX parameters (peak$\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope) showed no significant specificity and sensitivity.

The Cox regression model yielded the decisive parameters to proceed to reintervention as being a PRF ≥30% (HR 3,7; CI 1,7-8,3; p=0,001) and a RVEDVi ≥150 ml/m^2 (HR 3; CI 1,5-6; p=0,002) in the cardiac MR.

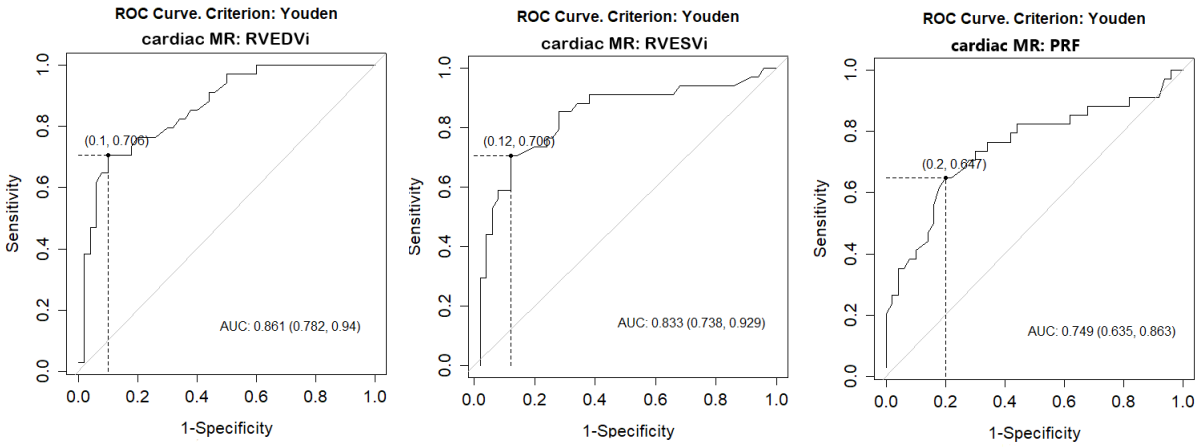

Figure 18: Receiver operating characteristics (ROC) curve of cardiac MR parameters: Sensitivity and specificty of RVEDVi (right ventricular enddiastolic volume indexed to BSA) on the left; sensitivity and specificty of RVESVi (right ventricular endsystolic volume indexed to BSA in the middle; sensitivity and specificty of PRF (pulmonary regurgitation fraction) on the right side.

5.4. The last follow-up

In this section all 97 patients (RI and NRI group) were evaluated (see Table 4). The average FU time after a corrective surgical repair was 26,7 ±8 (9-52) years for all patients. There was a tendency of a longer FU time in the RI group (NRI 24,9 ±8 (9-44) vs. RI 29,4 ±7 (15-52) years, p>0,05). The average age at the last FU was 29,9 ±9 (18-57) years without a notable difference between the two groups. In the RI group the time between the last reintervention and the latest FU was 5,3 ±4,3 (2-12,5) years on average.

At the last FU 83/97 (85,6%) patients formed part of the NYHA class I and the remaining 14/97 (14,4%) patients of the NYHA class II-III without a statistical difference between the two groups. Cardiac medication was more often prescribed in the RI group (26/38 (68,4) vs. 21/59 (35,6%), p=0,04). The mean NT-pro-BNP levels were in the normal range (<130 pg/ml) in the NRI group (103 ±78 (13-436) pg/ml) and showed a mild increase in the RI group (150 ±107 (20-412) pg/ml) without significant differences between the two groups. The QRS duration did not differ significantly between both groups (NRI 149 ±20 (100-180) vs. 153 ±25 (90-206), p>0,05). Nonetheless, the QRS duration was found to be directly related to an increase in RV volumes (RVEDVi p=0,03; RVESVi p<0,001) and the severity of the PR (PRF p=0,04) and inversely related to a reduced systolic RV (RV-EF <0,001) and the LV function (LV-EF p<0,001) in the cardiac MR. Therapeutic relevant arrhythmias were observed in 25/97 (25,8%) patients. Patients with arrhythmia were significantly older (36,6 ±11 (18,5-58) years,) than those patients without arrhythmia (28,2 ±10 [18-44,5] years, p=0,032). Fifteen patients were treated medically whereas 6 patients underwent a PM and 4 patients an ICD implantation.

At the last FU a moderate or severe PR was assessed in 44/97 (45%) patients in the echocardiography but found more often in the NRI than in the RI group (36/59 (61%) vs. 8/38 (21%), p=0,003). The systolic RV function measured by TAPSE was mildly reduced in all patients without a statistical significance between both groups (NRI 17,4 ±3 (10-25) vs. RI 15,5 ±3 (11-22) mm, p>0,05). Other echocardiographic parameters such as TI, severe PS, RV Dm and LV-EF showed no significant difference in both groups. Cardiac MR showed a normally ranged mean value of the systolic RV and the LV function and the RV volumes in both groups (see Table 4). However, 40/97 (41,2%) of all patients showed a reduced (<45%) RV-EF. Similar to the results in echocardiography, a significant PR occurred more often in the NRI than in the RI group (PRF 23 ±17 (0-60) vs. 8 ±10 (0-40) %, p= 0,004).

Overall in the analysis the parameters of the CPX showed no statistical significance between the groups. However, a normally ranged (≥85%) max. workload pred was seen in 41/97 (42,3%) and a normally ranged (≥85%) peak$\dot{V}O_2$ pred in 46/97 (47,4%) patients.

	NRI, n=59	**after RI,** n=38	**p-value**	**all patients**, n=97
age at last FU [years]	28,3 ±9 (18-54)	32,5 ±8 (20-57)	>0,05	29,9 ±9 (18-57)
time of FU at last FU [years]	24,9 ±8 (9-44)	29,4 ±7 (15-52)	>0,05	26,7 ±8 (9-52)
NYHA class I	52/59 (88,1%)	31/38 (81,6%)	>0,05	83/97 (85,6%)
NYHA class II-III	7/59 (11,9%)	7/38 (18,4%)		14/97 (14,4%)
medication	21/59 (35,6%)	26/38 (68,4)	**0,04**	47/97 (48,5%)
QRS duration [msec]	149 ±20 (100-180)	153 ±25 (90-206)	>0,05	150 ±22 (90-206)
NT-pro BNP [pg/ml]	103 ±78 (13-436)	150 ±107 (20-412)	>0,05	143 ±93 (13-436)
echocardiography				
RV Dm (apical 4-ch view) [mm]	41 ±8 (27-58)	41 ±7 (29-58)	>0,05	41 ±7 (27-58)
TAPSE [mm]	17,4 ±3 (10-25)	15,5 ±3 (11-22)	>0,05	16,6 (10-25)
PR none, mild	23/59 (39%)	30/38 (79%)	**0,003**	53/97 (54,6%)
PR moderate, severe	36/59 (61%)	8/38 (21%)		44/97 (45,4%)
PS >36mmHg	3/59 (5,1%)	0/38 (0%)	>0,05	3/97 (3%)
TI none, mild	53/59 (89,9%)	33/38 (86,8%)	>0,05	86/97 (88,7%)
TI moderate, severe	6/59 (10,2%)	5/38 (13,2%)		11/97 (11,3%)
LV-EF [%]	59 ±6 (45-79)	60 ±8 (45-74)	>0,05	59 ±7 (45-74)
cardiac MR				
RVEDVi [ml/m^2]	114 ±29 (68-235)	104 ±27 (71-194)	>0,05	110 ±29 (68-235)
RVESVi [ml/m^2]	63 ±24 (33-185)	59 ±24 (33-130)	>0,05	61 ±24 (33-185)
RV-EF [%]	46 ±8 (20-60)	46 ±8 (30-70)	>0,05	46 ±8 (20-70)
PRF [%]	23 ±17 (0-60)	8 ±10 (0-40)	**0,004**	17 ±17 (0-60)
PS > 36mmHg	3/59 (5,1%)	0/38 (0%)	>0,05	3/97 (3%)
LF-EF [%]	57 ±8 (30-80)	59 ±7 (40-80)	>0,05	58 ±8 (30-80)
spiroergometry				
max. HR [bpm]	170 ±18 (121-194)	167 ±16 (130-187)	>0,05	166 ±22 (121-194)
max. HR pred [%]	88 ±10 (60-100)	90 ±10 (70-100)	>0,05	89 ±10 (60-100)
max. workload [W/kg]	2,3 ±0,6 (0,6-3,9)	2,2 ±0,4 (1,6-3,1)	>0,05	2,2 ±0,6 (0,6-3,1)
max. workload pred	85 ±17 (50-130)	86 ±15 (70-120)	>0,05	85 ±16 (50-130)
peak$\dot{V}O_2$ [ml/kg/min]	31,4 ±9 (18,4-53,6)	28,2 ±7 (18,5-46)	>0,05	29,8 ±8 (18,4-53,6)
peak$\dot{V}O_2$ pred [%]	86 ±19 (50-140)	84 ±19 (50-150)	>0,05	85 ±19 (50-150)
$\dot{V}E/\dot{V}CO_2$ slope	25,3 ±3,3 (21-35)	25,1 ±3,1 (18-33)	>0,05	25,2 ±3,2 (18-35)
FVC [l]	4,2 ±3,3 (2,2-6,3)	3,9 ±1,3 (2-6,1)	>0,05	4 ±1,1 (2-6,3)
FVC pred [%]	95 ±14 (60-130)	88 ±15 (60-110)	>0,05	92 ±15 (60-130)

Table 4: Comparison of patients without reintervention (NRI group) ≥18 years vs. patients with reintervention (RI group) ≥18 years at last follow-up (FU) in NRI and RI group. Abbreviations: RV (right ventricle), RV Dm (RV diameter), 4-ch (4 chamber view), TAPSE (tricuspid annular plane systolic excursion), PR (pulmonary regurgitation), PS (pulmonary stenosis), TI (tricuspid valve insufficiency), LV-EF (left ventricular ejection fraction), RVEDVi (right ventricular enddiastolic volume indexed to body surface area [BSA]), RVESVi (right ventricular endsystolic volume indexed to BSA), RV-EF (right ventricular ejection fraction), PRF (pulmonary regugritation fraction), HR (heart rate), pred (of predicted values).

6. Discussion

Residual intracardiac shunts, increased RV volumes, chronic pulmonary and TR, RV hypertension and arrhythmia might all together lead to cardiac remodelling and worsen clinical outcomes at later stages after a corrective surgical repair. (6,35,141) Thus, long-term FU of rTOF patients in adult life may provide insight for the treatment of future patients. In this section our long-term results are discussed in the context of the current state of the art in literature.

The number of TOF patients included in comparable studies in literature ranges from 59 – 977. (39,53,143–146,57,65,82,104,114,127,128,142) Our study population consisted of 97 patients. In our study the average FU time was 26,7 ±8 years which is longer than in the majority of studies reporting on a long-term FU of 5 - 21 years (39,53,143–146,57,65,82,104,114,127,128,142). Only the studies of *Nollert G et al*. (147) with 36 years of FU time and *Cuypers et al.* (19) with 40 years of FU time interval exceeded the duration of the FU presented herein.

In the most recent long-term studies changes over time in the cardiac MR have been predominately investigated either combined with echocardiography, QRS duration and/ or the clinical condition (NYHA class). In our study we aimed at comparing all available results assessed during routine examinations (clinical assessment, ECG, echocardiography, cardiac MR, CPX and NT-pro BNP). Studies including the same examinations as ours are rare in literature. (19,68,148,149)

During the FU almost 40% of our patients (38/97) proceeded to a reintervention including a PM/ ICD implantation at a mean of 24,2 ±7,7 years after the corrective surgical repair. In the large meta-analysis of *Ferraz Cavalcanti et al*. (150) including more than 3100 TOF patients the average time interval from the corrective surgical repair until the reintervention was largely scattered over the range of 9 - 28 years. Coherent with our results *Bokma JP et al.* (143) and *Graham TP et al.* (129) showed an average time interval of 26 years.

Since most late sequalae derive from a longstanding PR leading to RVOT dysfunction, the majority of reinterventions (81,1%, [43/53]) consisted of RVOT reconstructions in our study group as well. (18,126,129,142,143,150–152).

Indications for a RVOT reconstruction are still under debate and vary widely depending on the institutional approach. (53,75,126,142,153–155). In the to date largest prospective study of *Bokma JP et al.* (143) comprising 977 patients from the INDICATOR registry (an international multicentre TOF registry), RVOT reconstruction was performed if the following criteria were met: PRF >25% and ≥2 of the latter - RVEDVi >160 ml/m^2, RVESVi >80ml/m^2, RV-EF <47%, LV-EF <55% in the cardiac MR and a QRS duration >160 msec. During the FU a total of 440/977 (45%) patients underwent PVR, including 396/440 (90%) surgical and 44/440 (10%) percutaneous procedures at an average age of 26 ±15 years. Thus, reintervention was performed regardless of the symptoms.

Our criteria for the RVOT reconstruction are comparable to the cut-off values mentioned above with a RVEDVi ≥150 ml/m^2 and a PRF ≥30% in the cardiac MR. Regarding the technique chosen for the reintervention (n=53) there were 31 surgical, 12 transcatheter and 10 PM/ ICD interventions performed in 38/97 (39,2%) of our patients.

Nonetheless, the current guidelines of the European Society of Cardiology (55) and the American Heart Association/ American College of Cardiology (62) differentiate between symptomatic and asymptomatic patients for the indication of reintervention. In symptomatic patients with severe RV dilation and dysfunction, RVOT reconstruction, including PVR, can effectively reduce RV volumes. (55,62,151) In asymptomatic patients, however, the optimal timing and benefit of this reintervention remains uncertain despite intense interest and numerous publications on this topic. (6,55,61,62,156) Several studies tried to identify preoperative RV volumes thresholds to reach postoperative normalization of RV volumes and function following PVR. (35,126,141,142,152) In the meta-analysis of *Ferraz Cavalcanti PE et al.* (150) a RVEDVi >150 ml/m^2 and/ or RV-EF <45% was shown to have lost its capability of improving its function after a PVR. Another recent large multicentre observational cohort study from *Geva T et al.* (156) identified pre-PVR RV hypertrophy and dysfunction as well as an older age at the PVR as predictors of a shorter time until death or a sustained VT after PVR. These findings led to the suggestion that the PVR should be performed even in asymptomatic patients to prevent severe RV dysfunction and to reduce the risk of arrhythmias. Nevertheless, every method of the RVOT reconstruction, except for

the mechanical valve implantation has a limited durability and requires a repeat reintervention. Furthermore, the PVR is associated with various late risks such as a prosthetic valve deterioration over time and endocarditis. Every additional incision of the myocardium may initiate new substrates for arrhythmia. Percutaneous PVR may avoid some of these risk factors. (143) Apart from that patients with a moderate RV dilation and dysfunction who might be considered for an early PVR are at low risk for adverse events or progressive RV and LV dysfunction if managed conservatively. Hence, optimal timing and specific criteria for a PVR continue to be debated until to date. (82,95,143,150,156)

Following the RVOT reconstruction our study patients showed a significant reduction in diastolic as well systolic RV volumes and severity of PR whereas the systolic RV function increased significantly in the cardiac MR. Furthermore, levels of the NT-pro BNP decreased significantly after a RVOT reintervention. Systolic LV function, resting QRS duration, NYHA class and CPX parameters were unaffected by a reintervention.

Our results are in line with several other studies reporting on a significant reduction of RV volumes and the severity of PR as well as on an improvement of the systolic RV function after the RVOT reconstruction. (57,126,142,157) Regarding the biventricular response to the RVOT reconstruction, systolic LV function improved in some studies (126,151,158) but didn't change in others (154,157). In our patient group the LV systolic function was only mildly reduced before the RVOT reintervention and showed a small, but insignificant improvement afterwards (56 ±8 vs. 59 ±7, p>0,05).

According to the meta-analysis of *Ferraz Cavalcanti et al.* (150), the NYHA class generally improves after the reintervention. In our study, however, no significant difference became apparent following the reintervention. Since most of our patients could be classified in the NYHA class I or II before the reintervention, the changes after reintervention resulted in no statistically significant effect (NYHA class I/ II before 27/38 patients vs. 31/38 after reintervention).

As reported by *Eindhoven et al*. (77) our study showed increased levels of NT-pro BNP exhibited by 50% of the rTOF patients correlated with age. A significant correlation between increased NT-pro BNP levels, the severity of PR and the

postoperative decrease was reported in *Dodge-Kathami A et al*. (159) and *Koch et al.* (80).

The development of cardiac arrhythmias is a well-known late complication in rTOF patients. (18,19,35,65,144) In the studies of *Cuypers et al.* (19) and *Babu-Narayan et al.* (148), the cumulative occurrence of symptomatic arrhythmias ranged between 17% - 21% at an average age of 35 years. In the most recent largest multicentre study of *Khairy P et al.* (71) including 556 patients, atrial arrhythmias were found in 20.1% and ventricular arrhythmias in 14.6% of rTOF patients aged 36,8 ±12 years. According to *Khairy P et al.* (71) and others (35,65,71,144), risk factors associated with arrhythmia in long-term FU are the RV enlargement, the number of cardiac surgeries, and older age at corrective surgical repair as well as advancing age in general. In *Khairy P et al.* (71), 46,6% of the patients had underwent previous palliative procedures and in 80,4% patients a transannular patch plasty at the corrective surgical repair was performed. At an average age of 36,8 ±12 years the patients of this study had undergone a mean of 2,5 cardiac surgeries.

In our study population about 25% of patients showed therapeutic relevant arrhythmias requiring 10 PM/ ICD implantations and antiarrhythmic treatment in 15 patients. Compared to *Khairy P et al.* (71) our patients had undergone less reinterventions at the time of the last FU (1,4 per patient) and had less palliative shunts (34/97 [35,1%]). Only 47/97 (48,5%) patients had undergone a transannular patch plasty during the corrective surgical repair. However, compared to the patients with a SR, our patients with arrhythmia were significantly older (mean age of 36,6 ±11 years [p=0,032]).

Gatzoulis et al. (65) reported a resting QRS duration ≥180 msec as an independent risk factor for VT and sudden cardiac death. In contrast we found in our study that only 6/97 (6,2%) patients showed a QRS prolongation ≥180 msec, the average being 150 ±22 msec. As reported in other studies, the QRS duration in our patients remained unaffected by a reintervention but correlated significantly with increased RV volumes, the severity of PR and a reduced RV and LV systolic function. (70,158,160)

In our study transannular patch plasty at the corrective surgical repair was performed in 47/97 (48,5%) patients with a tendency of higher occurrence in the patients already undergone reintervention (HR 1,76; CI 0,90 – 3,43; p>0,05). This might be a limitation of our relatively small patient group as compared to others. The use of transannular patch is a well-known risk factor for a severe PR, RVOT dysfunction and arrhythmia in the long term and showed in our study just a tendency without statistical significance. (6,63,65,141) Another risk factor for a repeat intervention is the naturally advancing age. As reported in *Geva et al.* (141), the prevalence of complications in patients triple during the third postoperative decade and beyond (18,64,65,116,147) In our patient group a trend for a longer FU duration in patients having undergone reinterventions became evident: At the last FU patients having already undergone a reintervention were on average 4 years older than those without a reintervention during adult life (24,9 ±8 vs. 29,4 ±7 years [p=0,056]).

As shown in other studies the CPX assessment plays an important role for the long-term management of GUCH patients. (55,62,68,70,97,104,148,161) For instance, *Müller J et al.* (97) showed in their multicentre study of 875 rTOF patients of an average of 25,5 ±12 years old and a mean FU time of 4,1 years that a peak$\dot{V}$O2 pred ≤65% and a $\dot{V}E/\dot{V}CO_2$ slope ≥31 are independent predictors of death, sustained VT, and event-free survival. Moreover, according to recent literature, a RVOT reconstruction has only very limited effect on the exercise capacity (peak$\dot{V}O_2$), but an increasing age significantly reduces the exercise capacity of rTOF patients compared to their healthy age group. (143,152,162)

In our patient group, no significant differences throughout the time of the FU were found. One reason might be that our patient group (n=97) was too small to show significant statistical differences in the CPX. At the last FU the peak$\dot{V}O_2$ pred was largely scattered over our patient group (peak$\dot{V}O_2$ pred with a median of 85, ranging between 47 and 145 %), rendering it impossible to draw significant conclusions. Our results of the $\dot{V}E/\dot{V}CO_2$ slope showed a normal distribution with a mean $\dot{V}E/\dot{V}CO_2$ slope of 25,2 ±3,2 (18-35). *Müller J et al.* (97) reported on a $\dot{V}E/\dot{V}CO_2$ slope ≥31 to predict risk factors for morbidity and mortality. Thus, for a statistically significant conclusion a larger patient group in haemodynamically more critical conditions might be necessary. In addition, in our study several

investigators contributed during the FU time interval of more than 26 years. For both studies of *Müller J et al.* (97) and *Kalaitzidis P et al.* (70) patients were recruited prospectively.

At the last FU our patients were on average 29,9 ±9 years old and were in good clinical conditions - given the circumstances. Most patients could be classified in the functional NYHA class I (NYHA class I 85,6%, NYHA class II/ III 14.4%). Their systolic RV and LV function was within the healthy range, only the RV volumes were mildly increased but without a significant difference between the patients having already undergone reintervention to those without any reintervention during adult life. The only difference marked the severity of PR showing better results in the reintervention group. Furthermore, cardiac medication was more often prescribed in the reintervention group as could be expected. The levels of the NT-pro BNP were mildly increased without any differences between the two groups. These results at the last FU clearly show an equalization of the investigated parameters among both groups and thereby prove the positive effect of a performed reintervention.

Study limitations: First, this study is limited by its retrospective approach. Therefore, a non-negligible number of rTOF and PA/ VSD patients had to be excluded of the analysis due to insufficient data acquisition. Another disadvantageous fact is that no further data of the development of the patients lost for the FU was acquired (i.e. premature/ sudden cardiac death, or other reasons). This missing data negatively impacts the significance of the obtained results. Hence the analysis of this conducted study is focused on the current condition of those patients who are in a regular FU at our clinic. Thus, it is possible that a selection bias is present, resulting in important differences between the patients.

A long FU time implies various contributing surgeons and different surgical techniques due to advances over the course of the FU time (i.e. the length of the RV incision, the use of a transannular patch, the extent of infundibular muscle resection, the method of surgical reconstruction of the pulmonary valve). For instance, 53/97 (54,6%) patients of our study population had undergone a corrective surgical repair <1990. Moreover, the implementation of cardiac MR, new

techniques in echocardiography, and the NT-pro BNP value as a routine predictive tool for a RV dysfunction for the standard FU examination may all have played a role in the analysis. Again, there were many different investigators involved in assessing our patients' condition. Concerning the CPX, it can be stated that clinical experience is crucial for in the management of GUCH patients. Despite the development of GUCH outpatient clinics, one has to note that CPX, in particular spiroergometry is still a very recently developed approach for a routine FU of rTOF patients. These constraints must be taken into account when analysing a FU duration of over 26 years. However, these limitations reflect the clinical reality.

Conclusion: The clinical condition of patients with repaired TOF and PA/ VSD was excellent more than 26 years after a corrective surgical repair. In approximately 40% of our patients a reintervention was performed in adult life during the FU interval. Among the approaches included in the FU examinations, cardiac MR has proven itself as the most reliable one to decide on the necessity of a reintervention.

It was found that most complications late after the corrective surgical repair originate from the sequalae of the RVOT. As an outlook future research should be focused on the development of long-term solutions for RVOT reconstructions to minimize a repeat reintervention.

7. References

1. Macmahon B, Mckeown T, Record R. The incidence and life expectation of children with congenital heart disease. Br Heart J. 1953 Apr;15(2):121–9.

2. Hoffman JIE, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39(12):1890–900.

3. Van Der Linde D, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, et al. Birth Prevalence of Congenital Heart Disease Worldwide. JAC. 2011;58:2241–7.

4. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime Prevalence of Congenital Heart Disease in the General Population From 2000 to 2010. Circulation. 2014 Aug 26;130(9):749–56.

5. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing Mortality in Congenital Heart Disease. J Am Coll Cardiol. 2010;56(14):1149–57.

6. Apitz C, Webb GD, Redington AN. Tetralogy of Fallot. Lancet. 2009;374(9699):1462–71.

7. Webb GD, Smallhorn JF, Therrien J, Redington AN. Congenital Heart Disease. In: Mann DL, editor. Braunwald's heart disease: a textbook of cardiavascular medicine. 10th ed. Philadelphia: Elsevier Inc. Saunders; 2015. p. 1392–443.

8. Schwedler G, Lindinger A, Lange PE, Sax U, Olchvary J, Peters B, et al. Frequency and spectrum of congenital heart defects among live births in Germany: A study of the competence network for congenital heart defects. Clin Res Cardiol. 2011;100(12):1111–7.

9. van der Bom T, Mulder BJ, Meijboom FJ, van Dijk AP, Pieper PG, Vliegen HW, et al. Contemporary survival of adults with congenital heart disease. Heart. 2015;101(24):1989–95.

10. Danielson GK, Dore A, Harris L, Hoffman JIE, Somerville J, Williams RG, et al. Task Force 1: the changing profile of congenital heart disease in adult life. Vol. 37, Journal of the American College of Cardiology. 2001.

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

12. Orwat MI, Kempny A, Bauer U, Gatzoulis MA, Baumgartner H, Diller G-P. The importance of national and international collaboration in adult congenital heart disease: A network analysis of research output. Int J Cardiol. 2015 Sep 15;195:155–62.

13. Mylotte D, Pilote L, Ionescu-Ittu R, Abrahamowicz M, Khairy P, Therrien J, et al. Specialized Adult Congenital Heart Disease Care. Circulation. 2014 May 6;129(18):1804–12.

14. Hörer J. Current spectrum, challenges and new developments in the surgical care of adults with congenital heart disease. Cardiovasc Diagn Ther. 2018 Dec;8(6):754–64.

15. Goossens E, Stephani I, Hilderson D, Gewillig M, Budts W, Van Deyk K, et al. Transfer of adolescents with congenital heart disease from pediatric cardiology to adult health care: An analysis of transfer destinations. J Am Coll Cardiol. 2011;57(23):2368–74.

16. Diller G-P, Breithardt G, Baumgartner H. Congenital heart defects in adulthood. Dtsch Arztebl Int. 2011 Jul;108(26):452–9.

17. Mouws EMJP, de Groot NMS, van de Woestijne PC, de Jong PL, Helbing WA, van Beynum IM, et al. Tetralogy of Fallot in the Current Era. Semin Thorac Cardiovasc Surg. 2019 Sep 1;31(3):496–504.

18. Dennis M, Moore B, Kotchetkova I, Pressley L, Cordina R, Celermajer DS. Adults with repaired tetralogy: Low mortality but high morbidity up to middle age. Open Hear. 2017;4(1).

19. Cuypers JAAE, Menting ME, Konings EEM, Opić P, Utens EMWJ, Helbing WA, et al. Unnatural history of tetralogy of fallot: Prospective follow-up of 40 years after surgical correction. Circulation. 2014;130(22):1944–53.

20. Rauch R, Hofbeck M, Zweier C, Koch A, Zink S, Trautmann U, et al. Comprehensive genotype-phenotype analysis in 230 patients with tetralogy of Fallot. J Med Genet. 2010;47(5):321–31.

21. Herold G. Die Fallotsche Tetralogie im Erwachsenenalter. In: Herold Gerd, editor. Herold Innere Medizin. Köln; 2018. p. 194–7.

22. Morris J, Springett A, Greenlees R, Loane M, Addor M-C, Arriola L, et al. Trends in congenital anomalies in Europe from 1980 to 2012. PLoS One. 2018;13(4):1–18.

23. Kliegman RM, Stanton BF, St. Geme III JW, Schor NF. Nelson's Textbook of Pediatrics. 20th ed. Vol. 2, Nelson's Textbook of Pediatrics. Philadelphia: Elsevier; 2016. 3888 p.

24. Brade T, Pane LS, Moretti A, Chien KR, Laugwitz KL. Embryonic heart progenitors and cardiogenesis. Cold Spring Harb Perspect Med. 2013;3(10):1–17.

25. Lopez-Sanchez C, Garcia-Masa N, Gañan CM, Garcia-Martinez V. Movement and commitment of primitive streak precardiac cells during cardiogenesis. Int J Dev Biol. 2009;53(8–10):1445–55.

26. Kloesel B, DiNardo JA, Body SC. Cardiac Embryology and Molecular Mechanisms of Congenital Heart Disease: A Primer for Anesthesiologists. Anesth Analg. 2016;123(3):551–69.

27. Srivastava D, Olson EN. A genetic blueprint for cardiac development. Nature. 2000 Sep;407(6801):221–6.

28. Morgenthau A, Frishman WH. Genetic Origins of Tetralogy of Fallot. Cardiol Rev. 2018;26(2):86–92.

29. Lindsey SE, Butcher JT, Yalcin HC. Mechanical regulation of cardiac development. Front Physiol. 2014;5(318).

30. Gortner L, Meyer S, Sitzmann FC. Duale Reihe Pädiatrie. 4th ed. Gortner L, Meyer S, Sitzmann FC, editors. Stuttgart: Duale Reihe; 2012. 331–345 p.

31. Brockmeier K, Hoppe UC. Angeborene Herzfehler im Erwachsenenalter. In: Erdmann E, editor. Klinische Kardiologie. 8th ed. Heidelberg: Springer Medizin Verlag; 2011. p. 406–24.

32. Chikwe J, Cooke D, Weiss A. Congenital surgery. In: Chikwe J, Cooke D, Weiss A, editors. OSH Cardiothoracic Surgery. 2nd ed. Oxford University Press; 2013. p. 521–642.

33. Oliveira PHA, Souza BS, Pacheco EN, Menegazzo MS, Corrêa IS, Zen PRG, et al. Genetic Syndromes Associated with Congenital Cardiac Defects and Ophthalmologic Changes - Systematization for Diagnosis in the Clinical Practice. Arq Bras Cardiol. 2018;110(1):84–90.

34. Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, et al. Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004-2006. Birth Defects Res A Clin Mol Teratol. 2010 Dec;88(12):1008–16.

35. Villafañe J, Feinstein JA, Jenkins KJ, Vincent RN, Walsh EP, Dubin AM, et al. Hot topics in tetralogy of fallot. J Am Coll Cardiol. 2013;62(23):2155–66.

36. Michielon G, Marino B, Formigari R, Gargiulo G, Picchio F, Digilio MC, et al. Genetic Syndromes and Outcome After Surgical Correction of Tetralogy of Fallot. Ann Thorac Surg. 2006;81:968–75.

37. Starr JP. Tetralogy of Fallot: Yesterday and Today. World J Surg. 2010 Apr 29;34(4):658–68.

38. Hallman GL, Leachman RD, Ochsner JL. Tetralogy of Fallot: The First 300 Years. Texas Hear Inst J. 1994;21:272–9.

39. Diaz-Frias J, Guillaume M. Tetralogy of Fallot. In: National Library of Medicine. StatPearls Publishing LLC; 2018.

40. Loukas M, Cesmebasi A, Le D, Etienne D, Tubbs RS, Anderson RH. Etienne-Arthur Louis Fallot and his tetralogy. Clin Anat. 2014 Oct 1;27(7):958–63.

41. Gatzoulis MA, Webb GD, Daubeney PEF. Diagnosis and management of adult congenital heart disease. 1st ed. Gatzoulis MA, editor. Elsevier; 2001. 315–334 p.

42. Califf RM, Prystowsky EN, Thomas JD, Thompson PD. Textbook of Cardiovascular Medicine. 3rd ed. Topol EJ, editor. Philadelphia: Lippincott Williams & Wikins; 2007. 1664 p.

43. Jordan SC, Scott O. Heart Disease in Paediatrics. 3rd ed. Oxford: Butterworth-Heinemann; 1989. 374 p.

44. O'Gara PT, Loscalzo J. Vorgehen beim Patienten mit Herzgeräusch. In: Suttorp N, Möckel M, Sigmund B, Dietel M, editors. Harrisons Innere Medizin. 19th ed. Berlin: ABW Wissenschaftsverlag; 2016. p. 4542.

45. Adamson D, Dhanjal M, Nelson-Piercy C. Cyanotic heart disease. In: Adamson D, Dhanjal M, Nelson-Piercy C, editors. Heart Disease in Pregnancy (Oxford Specialist Handbooks in Cardiology). 1st ed. Oxford Medicine Press; 2011. p. 166–70.

46. Karas MG, Kizer JR. Echocardiographic assessment of the right ventricle and associated hemodynamics. Prog Cardiovasc Dis. 2012;55:144–60.

47. Davlouros PA, Niwa K, Webb G, Gatzoulis MA. The right ventricle in congenital heart disease. Heart. 2006 Apr;92 Suppl 1(Suppl 1):i27-38.

48. Chitra N, Vijayalakshmi IB. Fetal echocardiography for early detection of congenital heart diseases. J Echocardiogr. 2017;15(1):13–7.

49. Picazo-Angelin B, Zabala-Argüelles JI, Anderson RH, Sánchez-Quintana D. Anatomy of the normal fetal heart: The basis for understanding fetal

echocardiography. Ann Pediatr Cardiol. 2018;11(2):164–73.

50. Katritsis DG, Gersh BJ, Camm JA. Tetralogy of Fallot. In: Katritsis DG, Gersh BJ, Camm JA, editors. Clinical Cardiology: Current Practice Guidelines . Oxford University Press; 2016.

51. Bacchus L, Spindola-Franco H. Tetralogy of Fallot. In: White CS, Haramati LB, Jen-Sho Chen J, Levsky JM, editors. Cardiac Imaging. Oxford University Press; 2014.

52. Cunningham MEA, Donofrio MT, Murfad Peer S, Zurakowski D, Jonas RA, Sinha P. Optimal Timing for Elective Early Primary Repair of Tetralogy of Fallot: Analysis of Intermediate Term Outcomes. Annu Thorac Surg. 2017;103(3):845–52.

53. Mitropoulos FM, Kanakis MA, Ntellos C, Loukas C, Davlouros P, Kousi T, et al. Pulmonary valve replacement in patients with corrected tetralogy of Fallot. J Cardiovasc Thorac Res. 2017;9(2):71–7.

54. Townsley MM, Windsor J, Briston D, Alegria J, Ramakrishna H. Tetralogy of Fallot: Perioperative Management and Analysis of Outcomes. J Cardiothorac Vasc Anesth. 2019 Feb;33(2):556–65.

55. Baumgartner H, Bonhoeffer P, De Groot Natasja, de Haan F, Deanfield JE, Galie N, et al. ESC Guidelines for the management of grown-up congenital heart disease. Eur Heart J. 2010;31:2915–57.

56. Al Habib HF, Jacobs JP, Mavroudis C, Tchervenkov CI, O'brien SM, Mohammadi S, et al. Contemporary Patterns of Management of Tetralogy of Fallot: Data From The Society of Thoracic Surgeons Database. Ann Thorac Surg. 2010;90(3):813–20.

57. Sfyridis PG, Kirvassilis G V, Papagiannis JK, Avramidis DP, Ieromonachos CG, Zavaropoulos PN, et al. Preservation of right ventricular structure and function following transatrial-transpulmonary repair of tetralogy of Fallot. Eur J Cardiothorac Surg. 2013;43(2):336–42.

58. Ylitalo P, Nieminen H, Pitkänen OM, Jokinen E, Sairanen H. Need of transannular patch in tetralogy of Fallot surgery carries a higher risk of reoperation but has no impact on late survival: results of Fallot repair in Finland. Eur J Cardiothorac Surg. 2015;48(1):91–7.

59. Luijten LWG, Van Den Bosch E, Duppen N, Tanke R, Roos-Hesselink J, Nijveld A, et al. Long-term outcomes of transatrial-transpulmonary repair of tetralogy of Fallot. Eur J Cardio-Thoracic Surg. 2015;47(3):527–34.

60. Egbe AC, Mittnacht AJ, Nguyen K, Joashi U. Risk factors for morbidity in infants undergoing tetralogy of fallot repair. Ann Pediatr Cardiol. 2014 Jan;7(1):13–8.

61. Fuller S. Tetralogy of fallot and pulmonary valve replacement: Timing and techniques in the asymptomatic patient. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2014;17(1):30–7.

62. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, et al. 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Apr 2;139(14):e698–800.

63. Bowater S, Gatzoulis MA. Surgically-corrected tetralogy of Fallot and associated arrhythmias. In: Myat A, Haldar S, Redwood S, editors. Challenging Concepts in Cardiovascular Medicine: A Case-Based Approach with Expert Commentary. 1st ed. Oxford University Press; 2011. p. 205–14.

64. Geva T. Repaired tetralogy of Fallot: the roles of cardiovascular magnetic resonance in evaluating pathophysiology and for pulmonary valve replacement decision support. J Cardiovasc Magn Reson. 2011 Jan 20;13(1):9.

65. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet. 2000;356(9234):975–81.

66. Beurskens NEG, Hagdorn QAJ, Gorter TM, Berger RMF, Vermeulen KM, van Melle JP, et al. Risk of cardiac tachyarrhythmia in patients with repaired tetralogy of Fallot: a multicenter cardiac MRI based study. Int J Cardiovasc Imaging. 2019 Jan 9;35(1):143–51.

67. Probst J, Diller G-P, Reinecke H, Leitz P, Frommeyer G, Orwat S, et al. Prevention of sudden cardiac death in patients with Tetralogy of Fallot: Risk assessment and long term outcome. Int J Cardiol. 2018 Oct 15;269:91–6.

68. Luijnenburg SE, Helbing WA, Moelker A, Kroft LJM, Groenink M, Roos-Hesselink JW, et al. 5-year serial follow-up of clinical condition and ventricular function in patients after repair of tetralogy of Fallot. Int J Cardiol. 2013;169(6):439–44.

69. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and t. J Am Soc Echocardiogr. 2010;23:685–713.

70. Kalaitzidis P, Orwat S, Kempny A, Robert R, Peters B, Sarikouch S, et al. Biventricular dyssynchrony on cardiac magnetic resonance imaging and its correlation with myocardial deformation, ventricular function and objective exercise capacity in patients with repaired tetralogy of Fallot. Int J Cardiol. 2018;264:53–7.

71. Khairy P, Aboulhosn J, Gurvitz MZ, Opotowsky AR, Mongeon F-P, Kay J, et al. Arrhythmia Burden in Adults With Surgically Repaired Tetralogy of Fallot. Circulation. 2010 Aug 31;122(9):868–75.

72. Tretter JT, Friedberg MK, Wald RM, Mcelhinney DB. Defining and refining indications for transcatheter pulmonary valve replacement in patients with repaired tetralogy of Fallot: Contributions from anatomical and functional imaging. Int J Cardiol. 2016;221:916–25.

73. Amedro P, Picot MC, Moniotte S, Dorka R, Bertet H, Guillaumont S, et al. Correlation between cardio-pulmonary exercise test variables and health-related quality of life among children with congenital heart diseases. Int J Cardiol. 2016;203:1052–60.

74. Vigl M, Niggemeyer E, Hager A, Schwedler G, Kropf S, Bauer U. The importance of socio-demographic factors for the quality of life of adults with congenital heart disease. Qual Life Res. 2011;20(2):169–77.

75. Sabate Rotes A, Eidem BW, Connolly HM, Bonnichsen CR, Rosedahl JK, Schaff H V, et al. Long-Term Follow-Up After Pulmonary Valve Replacement in Repaired Tetralogy of Fallot. Am J Cardiol. 2014;6(114):901–8.

76. Bredy C, Ministeri M, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, et al. New York Heart Association (NYHA) classification in adults with congenital heart disease: Relation to objective measures of exercise and outcome. Eur Hear J - Qual Care Clin Outcomes. 2018;4(1):51–8.

77. Eindhoven JA, Menting ME, Van Den Bosch AE, Cuypers JAAE, Ruys TPE,

Witsenburg M, et al. Associations between N-terminal pro-B-type natriuretic peptide and cardiac function in adults with corrected tetralogy of Fallot. Int J Cardiol. 2014;174(3):550–6.

78. Hirono K, Sekine M, Shiba N, Hayashi S, Nakaoka H, Ibuki K, et al. N-terminal pro-Brain Natriuretic Peptide as a Predictor of Reoperation in Children With Surgically Corrected Tetralogy of Fallot. Circ J. 2014;78(3):693–700.

79. Paolino A, Hussain T, Pavon A, Velasco MN, Uribe S, Ordoñez A, et al. NT-proBNP as Marker of Ventricular Dilatation and Pulmonary Regurgitation After Surgical Correction of Tetralogy of Fallot: A MRI Validation Study. Pediatr Cardiol. 2017;38(2):324–31.

80. Koch AME, Zink S, Glöckler M, Seeliger T, Dittrich S. Plasma levels of B-type natriuretic peptide in patients with tetralogy of Fallot after surgical repair. Int J Cardiol. 2010;143(2):130–4.

81. Norozi K, Buchhorn R, Kaiser C, Hess G, Grunewald RW, Binder L, et al. Plasma N-terminal pro-brain natriuretic peptide as a marker of right ventricular dysfunction in patients with tetralogy of Fallot after surgical repair. Chest. 2005;128(4):2563–70.

82. Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. Am J Cardiol. 2005;95(6):779–82.

83. Pierard LA, Dulgheru RE. Evaluation of right ventricular function. In: Zamorano JL, Bax J, Knuuti J, Sechtem U, Lancellotti P, Badano L, editors. The ESC Textbook of Cardiovascular Imaging. 2nd ed. Oxford University Press; 2015. p. 336–51.

84. Maskatia SA, Morris SA, Spinner JA, Krishnamurthy R, Altman CA. Echocardiographic Parameters of Right Ventricular Diastolic Function in Repaired Tetralogy of Fallot Are Associated with Important Findings on Magnetic Resonance Imaging. Congenit Heart Dis. 2015;10(3):113–22.

85. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Hear J – Cardiovasc Imaging. 2015 Mar 1;16(3):233–71.

86. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic Assessment of Valve Stenosis : EAE / ASE Recommendations for Clinical Practice. J Am Soc Echocardiogr. 2008;22(5):1–23.

87. Huttin O, Voilliot D, Mandry D, Venner C, Juillière Y, Selton-Suty C. All you need to know about the tricuspid valve: Tricuspid valve imaging and tricuspid regurgitation analysis. Arch Cardiovasc Dis. 2016 Jan;109(1):67–80.

88. Dreyfus GD, Martin RP, Chan KMJ, Dulguerov F, Alexandrescu C. Functional tricuspid regurgitation: a need to revise our understanding. J Am Coll Cardiol. 2015 Jun 2;65(21):2331–6.

89. Arsalan M, Walther T, Smith RL, Grayburn PA. Tricuspid regurgitation diagnosis and treatment. Eur Heart J. 2015 Sep 10;38(9):634–8.

90. Renella P, Aboulhosn J, Lohan DG, Jonnala P, Finn JP, Satou GM, et al. Echocardiographic assessment of the right ventricle and associated hemodynamics. Prog Cardiovasc Dis. 2010 Apr;23(7):880–6.

91. Renella P, Aboulhosn J, Lohan DG, Jonnala P, Finn JP, Satou GM, et al. Two-

Dimensional and Doppler Echocardiography Reliably Predict Severe Pulmonary Regurgitation as Quantified by Cardiac Magnetic Resonance. Am Soc Echocardiogr. 2010;23(8):880–6.

92. Bonello B, Kilner PJ, Bonello B, Kilner PJ. Review of the role of cardiovascular magnetic resonance in congenital heart disease, with a focus on right ventricle assessment. Arch Cardiovasc Dis. 2012;105:605–13.

93. Kim YY, Ruckdeschel E. Approach to residual pulmonary valve dysfunction in adults with repaired tetralogy of Fallot. Heart. 2016;102(19):1520–6.

94. Blalock SE, Banka P, Geva T, Powell AJ, Zhou J, Prakash A. Interstudy variability in cardiac magnetic resonance imaging measurements of ventricular volume, mass, and ejection fraction in repaired tetralogy of fallot: A prospective observational study. J Magn Reson Imaging. 2013;38(4):829–35.

95. Lewis MJ, O'connor DS, Rozenshtien A, Ye S, Einstein AJ, Ginns JM, et al. Usefulness of Magnetic Resonance Imaging to Guide Referral for Pulmonary Valve Replacement in Repaired Tetralogy of Fallot. Am J Cardiol. 2014;114(9):1406–11.

96. Maceira AM, Prasad SK, Khan M, Pennell DJ. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. Eur Heart J. 2006;27(23):2879–88.

97. Müller J, Hager A, Diller G-P, Derrick G, Buys R, Dubowy K-O, et al. Peak oxygen uptake, ventilatory efficiency and QRS-duration predict event free survival in patients late after surgical repair of tetralogy of Fallot. Int J Cardiol. 2015;196:158–64.

98. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan S V., Broberg CS, et al. Exercise intolerance in adult congenital heart disease: Comparative severity, correlates, and prognostic implication. Circulation. 2005;112(6):828–35.

99. Myers J, Arena R, Cahalin LP, Labate V, Guazzi M. Cardiopulmonary Exercise Testing in Heart Failure. Curr Probl Cardiol. 2015;40(8):322–72.

100. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002 Mar 14;346(11):793–801.

101. Arena R, Sietsema KE. Exercise in Cardiovascular Disease Cardiopulmonary Exercise Testing in the Clinical Evaluation of Patients With Heart and Lung Disease. Circulation. 2011;(123):668–80.

102. Mantegazza V, Apostolo A, Hager A. Cardiopulmonary exercise testing in adult congenital heart disease. Ann Am Thorac Soc. 2017;14(17):S93–101.

103. Tan C, Rossiter HB, Porszasz J, Bowen TS, Witte KK, Stringer WW, et al. Reliability and Physiological Interpretation of Pulmonary Gas Exchange by "Circulatory Equivalents" in Chronic Heart Failure. J Am Heart Assoc. 2018 Apr 3;7(7).

104. Kipps AK, Graham DA, Harrild DM, Lewis E, Powell AJ, Rhodes J. Longitudinal exercise capacity of patients with repaired tetralogy of Fallot. Am J Cardiol. 2011;108(1):99–105.

105. Duppen N, Etnel JR, Spaans L, Takken T, van den Berg-Emons RJ, Boersma E, et al. Does exercise training improve cardiopulmonary fitness and daily physical activity in children and young adults with corrected tetralogy of Fallot or Fontan

circulation? A randomized controlled trial. Am Heart J. 2015;170(3):606–14.

106. Mercer-Rosa L, Zhang X, Tanel RE, Rychik J, Fogel MA, Paridon SM, et al. Perioperative Factors Influence the Long-Term Outcomes of Children and Adolescents with Repaired Tetralogy of Fallot. Pediatr Cardiol. 2018;39(7):1433–9.

107. Lawrenz W, Dubowy K-O, Baden W, Hager A. Ergometrie und Spiroergometrie bei Kindern und Jugendlichen. Arbeitsgemeinschaft für Belastungsuntersuchungen der Dtsch Gesellschaft für Pädiatrische Kardiol. 2019;75(3):399–413.

108. Haber P. Lungenfunktion und Spiroergometrie - Interpretation und Befunderstellung unter Einschluss der arteriellen Blutgasanalyse. 3rd ed. Wien: Springer-Verlag; 2013. 212 p.

109. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: A scientific statement from the American heart association. Circulation. 2013;128(8):873–934.

110. Beaver WL, Wasserman K, Whipp BJ, Whipp BJA. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol. 1986;60(6):2020–7.

111. Wasserman K, Stringer WW, Casaburi R, Koike A, Cooper CB. Determination of the anaerobic threshold by gas exchange: biochemical considerations, methodology and physiological effects. Z Kardiol. 1994;83 Suppl 3:1–12.

112. Mezzani A. Cardiopulmonary Exercise Testing: Basics of Methodology and Measurements. Ann Am Thorac Soc. 2017 Jul;14(Supplement 1):S3–11.

113. Thompson PD, Arena R, Riebe D, Pescatello LS. ACSM's New Preparticipation Health Screening Recommendations from ACSM's Guidelines for Exercise Testing and Prescription, Ninth Edition. Am Coll Sport Med. 2013;12 (4)(Current Sports Medicine Reports):215–7.

114. van den Berg J, Hop WC, Strengers JLM, de Jongste JC, van Osch-Gevers L, Meijboom FJ, et al. Clinical condition at mid-to-late follow-up after transatrial-transpulmonary repair of tetralogy of Fallot. J Thorac Cardiovasc Surg. 2007;133(2):470–7.

115. Coeckelberghs E, Buys R, Goetschalckx K, Cornelissen VA, Vanhees L. Prognostic value of the oxygen uptake efficiency slope and other exercise variables in patients with coronary artery disease. Eur J Prev Cardiol. 2016 Feb 29;23(3):237–44.

116. Murphy JG, Gersh BJ, Mair DD, Fuster V, McGoon MD, Ilstrup DM, et al. Long-Term Outcome in Patients Undergoing Surgical Repair of Tetralogy of Fallot. N Engl J Med. 1993 Aug 26;329(9):593–9.

117. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt O-A, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy The Task Force on cardiac pacing and resynchronization therapy of the. Eur Heart J. 2013;34:2281–329.

118. Chubb H, Neill MO, Rosenthal E. Device Therapy Pacing and Defibrillators in Complex Congenital Heart Disease. Arrhythm Electrophysiol Rev. 2016;5(1):57–64.

119. Egbe AC, Miranda WR, Madhavan M, Ammash NM, Venkata R, Al-otaibi M, et al. Cardiac implantable electronic devices in adults with tetralogy of Fallot. Heart. 2019;105(7):538–44.

120. Flügge A-K, Wasmer K, Orwat S, Abdul-Khaliq H, Helm PC, Bauer U, et al. Cardiac resynchronization therapy in congenital heart disease: Results from the German

National Register for Congenital Heart Defects. Int J Cardiol. 2018 Dec 15;273:108–11.

121. Midha D, Chen Z, Jones DG, Williams HJ, Lascelles K, Jarman J, et al. Pacing in congenital heart disease – A four-decade experience in a single tertiary centre. Int J Cardiol. 2017 Aug 15;241:177–81.

122. Santharam S, Hudsmith L, Thorne S, Clift P, Marshall H, De Bono J. Long-term follow-up of implantable cardioverter-defibrillators in adult congenital heart disease patients: indications and outcomes. Europace. 2016 May 26;19(3):407–13.

123. Kogon BE, Rosenblum JM, Mori M. Current Readings: Issues Surrounding Pulmonary Valve Replacement in Repaired Tetralogy of Fallot. Semin Thorac Cardiovasc Surg. 2015;27(1):57–64.

124. Head CEG, Thorne SA. Congenital heart disease in pregnancy. Postgrad Med J. 2005 May;81(955):292–8.

125. Thorne S, Bowater S. Lifestyle Issues. In: Thorne S, Bowater S, editors. Adult Congenital Heart Disease. 2nd ed. Oxford Medicine Press; 2017. p. 147–58.

126. Lee C, Kim YM, Lee CH, Kwak JG, Park CS, Song JY, et al. Outcomes of pulmonary valve replacement in 170 patients with chronic pulmonary regurgitation after relief of right ventricular outflow tract obstruction: Implications for optimal timing of pulmonary valve replacement. J Am Coll Cardiol. 2012;60(11):1005–14.

127. Meijer FMM, Kies P, Jongbloed MRM, Hazekamp MG, Koolbergen DR, Blom NA, et al. Excellent durability of homografts in pulmonary position analysed in a predefined adult group with tetralogy of Fallot. Interact Cardiovasc Thorac Surg. 2019;28(2):279–83.

128. Bokma JP, Winter MM, Oosterhof T, Vliegen HW, Van Dijk AP, Hazekamp MG, et al. Individualised prediction of pulmonary homograft durability in tetralogy of Fallot. Heart. 2015;101(21):1717–1723.

129. Graham TP, Bernard Y, Arbogast P, Thapa S, Cetta F, Child J, et al. Outcome of pulmonary valve replacements in adults after tetralogy repair: A multi-institutional study. Congenit Heart Dis. 2008;3(3):162–7.

130. Tatewaki H, Shiose A. Pulmonary valve replacement after repaired Tetralogy of Fallot. Gen Thorac Cardiovasc Surg. 2018;66:509–15.

131. Lurz P, Gaudin R, Taylor AM, Bonhoeffer P. Percutaneous Pulmonary Valve Implantation. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2009 Jan;12(1):112–7.

132. Bonhoeffer P, Boudjemline Y, Saliba Z, Merckx J, Aggoun Y, Bonnet D, et al. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. Lancet. 2000 Oct 21;356(9239):1403–5.

133. Esmaeili A, Bollmann S, Khalil M, De Rosa R, Fichtlscherer S, Akintuerk H, et al. Percutaneous pulmonary valve implantation for reconstruction of a patch-repaired right ventricular outflow tract. J Interv Cardiol. 2018 Feb;31(1):106–11.

134. Butera G, Milanesi O, Spadoni I, Piazza L, Donti A, Ricci C, et al. Melody transcatheter pulmonary valve implantation. Results from the registry of the Italian society of pediatric cardiology. Catheter Cardiovasc Interv. 2013 Feb;81(2):310–6.

135. Chatterjee A, Bajaj NS, McMahon WS, Cribbs MG, White JS, Mukherjee A, et al.

Transcatheter Pulmonary Valve Implantation: A Comprehensive Systematic Review and Meta-Analyses of Observational Studies. J Am Heart Assoc. 2017 Aug 2;6(8).

136. Nordmeyer J, Ewert P, Gewillig M, AlJufan M, Carminati M, Kretschmar O, et al. Acute and midterm outcomes of the post-approval MELODY Registry: a multicentre registry of transcatheter pulmonary valve implantation. Eur Heart J. 2019 Jul 14;40(27):2255–64.

137. McElhinney DB, Sondergaard L, Armstrong AK, Bergersen L, Padera RF, Balzer DT, et al. Endocarditis After Transcatheter Pulmonary Valve Replacement. J Am Coll Cardiol. 2018 Dec 4;72(22):2717–28.

138. Cheatham JP, Hellenbrand WE, Zahn EM, Jones TK, Berman DP, Vincent JA, et al. Clinical and hemodynamic outcomes up to 7 years after transcatheter pulmonary valve replacement in the US melody valve investigational device exemption trial. Circulation. 2015 Jun 2;131(22):1960–70.

139. Frigiola A, Hughes M, Turner M, Taylor A, Marek J, Giardini A, et al. Physiological and phenotypic characteristics of late survivors of tetralogy of fallot repair who are free from pulmonary valve replacement. Circulation. 2013;128(17):1861–8.

140. Breuer HW. Spiroergometrie - Vorschläge zur Standardisierung und Interpretation. Pneumologie. 2004 Aug;58(8):553–65.

141. Geva T. Indications for pulmonary valve replacement in repaired tetralogy of fallot: The quest continues. Circulation. 2013;128(17):1855–7.

142. Bokma JP, Winter MM, Oosterhof T, Vliegen HW, van Dijk AP, Hazekamp MG, et al. Preoperative thresholds for mid-to-late haemodynamic and clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. Eur Heart J. 2016 Mar;37(10):829–35.

143. Bokma JP, Geva T, Sleeper LA, Babu Narayan S V., Wald R, Hickey K, et al. A propensity score-adjusted analysis of clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. Heart. 2018;104(9):738–44.

144. Ait Ali L, Trocchio G, Crepaz R, Stuefer J, Stagnaro N, Siciliano V, et al. Left ventricular dysfunction in repaired tetralogy of Fallot: incidence and impact on atrial arrhythmias at long term-follow up. Int J Cardiovasc Imaging. 2016;32:1441–9.

145. Kutty S, Valente AM, White MT, Hickey K, Danford DA, Powell AJ, et al. Usefulness of Pulmonary Arterial End-Diastolic Forward Flow Late After Tetralogy of Fallot Repair to Predict a “Restrictive” Right Ventricle. Am J Cardiol. 2018;121(11):1380–6.

146. O’Meagher S, Munoz PA, Muthurangu V, Robinson PJ, Malitz N, Tanous DJ, et al. Mechanisms of maintained exercise capacity in adults with repaired tetralogy of Fallot. Int J Cardiol. 2014;177(1):178–81.

147. Nollert G, Fischlein T, Bouterwek S, Böhmer C, Klinner W, Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36- year follow-up of 490 survivors of the first year after surgical repair. J Am Coll Cardiol. 1997;30(5):1374–83.

148. Babu-Narayan S V., Diller GP, Gheta RR, Bastin AJ, Karonis T, Li W, et al. Clinical outcomes of surgical pulmonary valve replacement after repair of tetralogy of fallot and potential prognostic value of preoperative cardiopulmonary exercise testing. Circulation. 2014;129(1):18–27.

149. Egbe AC, Anavekar NS, Connolly HM. Abnormal Pulmonary Arterial Elastance Is

Associated With Reduced Exercise Capacity in Tetralogy of Fallot. J Am Heart Assoc. 2019 Jun 18;8(12):e011731.

150. Ferraz Cavalcanti PE, Sá MPBO, Santos CA, Esmeraldo IM, Escobar RR De, Menezes AM De, et al. Pulmonary valve replacement after operative repair of Tetralogy of Fallot: Meta-analysis and meta-regression of 3,118 patients from 48 studies. J Am Coll Cardiol. 2013;62(23):2227–43.

151. Quail MA, Frigiola A, Giardini A, Muthurangu V, Hughes M, Lurz P, et al. Impact of pulmonary valve replacement in tetralogy of fallot with pulmonary regurgitation: A comparison of intervention and nonintervention. Ann Thorac Surg. 2012;94(5):1619–26.

152. Frigiola A, Tsang V, Bull C, Coats L, Khambadkone S, Derrick G, et al. Biventricular Response After Pulmonary Valve Replacement for Right Ventricular Outflow Tract Dysfunction Is Age a Predictor of Outcome? Circulation. 2008;(118):S182-90.

153. Bhagra CJ, Hickey EJ, Van De Bruaene A, Roche SL, Horlick EM, Wald RM. Pulmonary Valve Procedures Late After Repair of Tetralogy of Fallot: Current Perspectives and Contemporary Approaches to Management. Can J Cardiol. 2017 Sep;33(9):1138–49.

154. Geva T, Gauvreau K, Powell AJ, Cecchin F, Rhodes J, Geva J, et al. Randomized trial of pulmonary valve replacement with and without right ventricular remodeling surgery. Circulation. 2010;122(11 SUPPL. 1):S201-8.

155. Meijboom FJ, Roos-Hesselink JW, McGhie JS, Spitaels SEC, van Domburg RT, Utens LMWJ, et al. Consequences of a selective approach toward pulmonary valve replacement in adult patients with tetralogy of Fallot and pulmonary regurgitation. J Thorac Cardiovasc Surg. 2008;135(1):50–5.

156. Geva T, Mulder B, Gauvreau K, Babu-Narayan S V., Wald RM, Hickey K, et al. Preoperative Predictors of Death and Sustained Ventricular Tachycardia After Pulmonary Valve Replacement in Patients With Repaired Tetralogy of Fallot Enrolled in the INDICATOR Cohort. Circulation. 2018;138:2106–15.

157. Heng EL, Gatzoulis MA, Uebing A, Sethia B, Uemura H, Smith GC, et al. Immediate and Midterm Cardiac Remodeling After Surgical Pulmonary Valve Replacement in Adults With Repaired Tetralogy of Fallot. Circulation. 2017 Oct 31;136(18):1703–13.

158. Chalard A, Sanchez I, Gouton M, Henaine R, Salami FA, Ninet J, et al. Effect of pulmonary valve replacement on left ventricular function in patients with tetralogy of fallot. Am J Cardiol. 2012;110(12):1828–35.

159. Dodge-Khatami A, Büchel EV, Knirsch W, Kadner A, Rousson V, Dave HH, et al. Brain Natriuretic Peptide and Magnetic Resonance Imaging in Tetralogy With Right Ventricular Dilatation. Ann Thorac Surg. 2006;82(3):983–8.

160. Wald RM, Valente AM, Gauvreau K, Babu-Narayan S V., Assenza GE, Schreier J, et al. Cardiac magnetic resonance markers of progressive RV dilation and dysfunction after tetralogy of Fallot repair. Heart. 2015;101(21):1724–30.

161. Paolillo S, Agostoni P. Prognostic Role of Cardiopulmonary Exercise Testing in Clinical Practice. Ann Am Thorac Soc. 2017 Jul 1;14(Supplement_1):53–8.

162. Bhat M, Mercer-Rosa L, Fogel MA, Harris MA, Paridon SM, Mcbride MG, et al. Longitudinal changes in adolescents with TOF: Implications for care. Eur Heart J Cardiovasc Imaging. 2017;18(3):356–63.

8. Appendix

Evaluation form