Long-term Follow-up in Cyanotic Congenital Heart Disease

Assessing determinants of outcome after the Fontan operation and Tetralogy of Fallot repair

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Lange termijn uitkomsten in cyanotische aangeboren hartafwijkingen

Determinanten van uitkomst na de Fontan operatie
en Tetralogie van Fallot operatie

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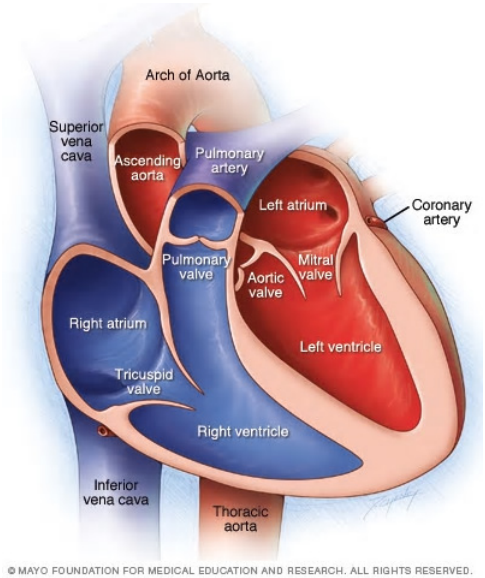
Chapter 1

General introduction and outline of this thesis

The heart, a muscular organ roughly the size of a fist, provides the body with oxygen and nutrients through the circulatory system. In the normal heart the venous blood from the body -with low oxygen saturation and high carbon dioxide levels - enters the right atrium (RA) and subsequently the right ventricle (RV). The RV supports the pulmonary circulation in which respiratory gas exchange takes place. The left ventricle (LV) supports the systemic circulation and ejects the high saturated blood towards the systemic arteries (Figure 1). The systemic circulation provides oxygenated blood to the brain, organs, muscles and other tissues. Beyond infancy, the pulmonary circulation and the systemic circulation are closed circuits.

Figure 1. Normal heart.



Congenital heart disease

In congenital heart defects (ConHD) there is a structural malformation of the heart and/or the intrathoracic great vessels.[1, 2] ConHD occur in approximately 8 per 1000 live births, which makes ConHD the most common birth defect.[1, 2] In the Netherlands, every year 1250-1400 children are born with a ConHD.[1, 3, 4]

There are many different types of ConHD, ranging from small atrial septal defects to severe and complex univentricular heart defects.[5-7] Often a division is made between non-cyanotic and cyanotic ConHD. In cyanotic ConHD the structural defects results in mixing of oxygen rich and poor oxygen blood.[6, 7] In case of a right-to-left shunt, the blood shunts from the right side to the left side of the heart. This situation creates a mix of oxygen poor and oxygen rich blood, resulting in oxygen desaturation in the

systemic arteries. The degree of arterial desaturation depends on the type of intracardiac mixing and the type of ConHD. Cyanosis is often a clinical sign in ConHD patients. Chronic cyanosis can result in vascular remodeling, erythrocytosis and hyperviscosity of the blood which can result in a decrease in the microcirculation.[5, 6, 8] Other symptoms of ConHD, depending on the type, are shortness of breath, excessive sweating, fatigue and failure to thrive.[5-7]

Long-term outcomes

Over the last decennia advances in diagnostics, catheter interventions, cardiothoracic surgery, pre- and (post)operative management and specialized care have contributed to a dramatic increase of survival in ConHD patients.[1] In the current era around 90% of ConHD children survive into adulthood,[9-11] which has now resulted in a population of adults with ConHD that is larger than the pediatric ConHD population.[12] However, frequently residual lesions remain, even after optimal surgical or catheter interventions. These residual abnormalities may result in pressure and/or volume overload of the ventricle and can contribute to long-term problems such as fatigue, diminished exercise tolerance, diminished ventricular function, chronic hypoxemia, arrhythmias and cardiac death.[13-15] Often ConHD patients require lifelong specialized medical care.[9] Particularly patients with complex ConHD have better outcomes when cared for in a multidisciplinary program.[9]

This thesis will particularly focus on two groups of patients with cyanotic heart diseases: patients with an univentricular heart defect and patients with a Tetralogy of Fallot (TOF). TOF is the most common cyanotic heart defect.[14, 16] In the Netherlands approximately 60 patients per year are born with TOF and require corrective surgery within the first few months of life.[14, 16] Patients with an univentricular heart defect are a heterogeneous group comprising approximately 10% of ConHD,[17] meaning that in the Netherlands approximately 125-140 patients a year are born with an univentricular heart defect.[16] Patients with an univentricular heart defect are among ConHD patients with the worst prognosis.

Etiology

In most ConHD patients the underlying cause for the ConHD is unknown and assumed to be multifactorial: a combination of predisposing genetic factors and environmental factors.[18-20] In a small number of patients a cause for the ConHD is found.

About 10% of all ConHD is explained by a chromosomal anomaly such as Down syndrome (Trisomy 21), Trisomy 13, Trisomy 18 or Turner syndrome (monosomy X).[21] Approximately 5% of TOF patients have Down syndrome.[22] Microdeletions and duplication such as 22q11 deletion syndrome and TBX5 gene mutations account for an estimated 15% of ConHD.[20, 23] 22q11 deletion syndrome is relatively common in TOF patients, with an estimated incidence of 15%.[24] The incidence of 22q11 deletion syndrome in patients with tricuspid atresia, an univentricular heart defect, is approximately 7%.[25] In some ConHD patients the cause of the heart defect lies in a

single abnormal gene (monogenic syndrome).[26] Even if no specific genetic cause for the ConHD is found, the recurrence risk for siblings and children of ConHD patients lies around 2-5%.[17] This suggests that more associated genes are waiting to be discovered. In the last decades several hundreds of genes have been identified that cause or contribute to the development of ConHD.[21, 23]

Some environmental factors have been linked to ConHD, explaining approximately 2% of the ConHD.[21] These include factors such as maternal exposure to lithium, folic acid antagonists, some selective serotonin reuptake inhibitors, maternal rubella infection and obesity.[20, 27, 28]

Univentricular heart defects

Univentricular heart defects are a group of different lesions that have in common that they have a functional single ventricle which supports both the systemic and pulmonary circulation at birth.[29] Often a relatively normal ventricle and an underdeveloped ventricle are present. In chapter 2 of this thesis an extensive overview is given on the surgical treatment options, management and outcomes of patients with an univentricular heart defect.

As in all other types of ConHD, univentricular hearts are described using the system of sequential segmental analysis. This includes thorough description of abdominal and atrial situs, atrio-ventricular connections and ventriculo-arterial connections.[17, 29, 30] The anatomy in univentricular heart defects is highly variable, ranging from tricuspid atresia to hypoplastic left heart syndrome (HLHS).[31, 32] In addition, in a significant proportion of patients with univentricular heart defects, abnormalities in the systemic venous and/or pulmonary venous connection are present, which makes the treatment of this patient group even more challenging.

The Fontan operation

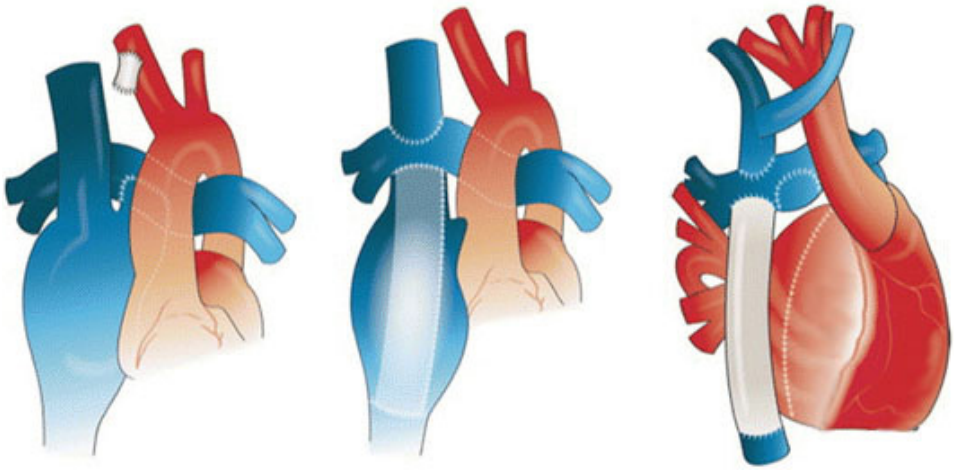
The natural history of patients with univentricular heart defect is poor. Depending on the underlying cardiac condition, the reported 1-year survival lies between 0-50%.[33-35] Before 1971, the year Francis Fontan published the paper '*Surgical repair of tricuspid atresia*', limited surgical options were available for univentricular heart defect patients.[36] Fontan proposed a separation of the pulmonary circulation and the systemic circulation by connecting the systemic venous return directly to the pulmonary arteries.[36] The Fontan circulation therefore bypasses a sub-pulmonary ventricle (i.e the RV in normal hearts) and solely relies on passive flow for pulmonary perfusion.

In the original Fontan operation the superior caval vein was connected to the right pulmonary artery (RPA) and the RA appendage was connected to the left pulmonary artery (LPA) with a valved conduit in a single procedure.[36] Over time several adaptations have been made to the original Fontan operation. Initially the atriopulmonary connection (APC) was used, in which the RA was connected directly to the pulmonary artery (see Figure 2).[37] The APC technique caused progressive dilatation of the RA and secondary chronic volume and pressure overload.[38] This atrial dilatation is associated

with thrombo-embolic events, compression of the pulmonary veins and arrhythmias.[38] Later, the modern Fontan procedure or the total cavopulmonary connection (TCPC) was described.[39] In the TCPC technique the superior caval vein is connected to the RPA with an end-to-side anastomosis.[39] Nowadays, there are two techniques to connect the inferior vena cava to the pulmonary arterial system. In 1988 the intra-atrial lateral tunnel (ILT) technique was described. The ILT was constructed with use of the posterior wall of the RA and a prosthetic patch to channel the inferior vena cava to the enlarged orifice of the transected superior vena cava that is anastomosed to the main pulmonary artery.[39] A couple years later the extracardiac conduit (ECC) technique was developed.[40] In the ECC technique the inferior vena cava is connected to the pulmonary arteries by using a Gore-Tex conduit (Figure 2).[40]

Originally the Fontan circuit was created in a single operation, resulting in a relatively high post-operative mortality.[13] Nowadays a staged TCPC procedure is clinical practice, in which a series of operations, in the course of a few years, creates the Fontan circuit.[13, 41] The type of first intervention depends on the underlying univentricular heart defect.[13] E.g. in case of a HLHS the single ventricle has to be connected to the aorta with the Norwood procedure.[13, 42] At approximately 3-6 months of age, the vena cava superior is connected to the pulmonary arteries creating a partial cavopulmonary connection (PCPC).[17] The TCPC is completed sometime between 18 months and 4 years of age, with an ECC or an ILT.[17, 43] When the Fontan circulation is completed a highly abnormal circulation is created in which a subpulmonary ventricle is lacking.[44, 45] This abnormal physiological state is characterized by an elevated systemic venous pressure and a decreased cardiac output.[44, 45]

Figure 2. Atrio-pulmonary Fontan, intra atrial lateral tunnel and extra cardiac conduit.
Adapted from Khairy et al.[17]



Long-term outcome

Since the development of the Fontan procedure, the long-time survival of Fontan patients increased from 69% 10-year survival in the cohort operated before 1990, to 95% 10-year survival in the patients receiving a Fontan after 2001.[46] Some researchers expect that the population of Fontan patients will double within 2 decades.[47]

Like mortality, the morbidity of the Fontan operation has declined over the last decades. However, long-term complications including circulatory failure, thromboembolic events, protein losing enteropathy (PLE), liver fibrosis and severe arrhythmias are common. These problems all relate to the highly abnormal physiological state in the Fontan circulation and/or to myocardial scars after extensive surgical procedures.[10, 43, 48, 49]

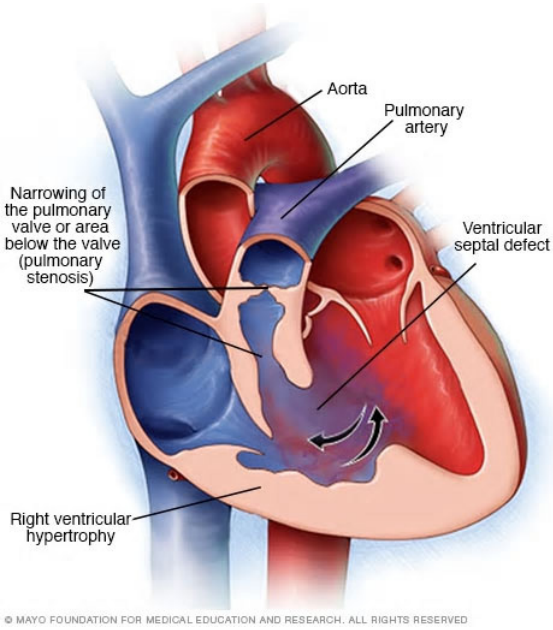
In ConHD patients, hospital admission for heart failure is an ominous sign with an one-year mortality of 24%.[50] In Fontan patients circulatory failure is relatively common during long-term follow-up.[45] The morphological abnormal functional single ventricle has been stressed for years through abnormal hemodynamic conditions, which potentially lead to diastolic and systolic dysfunction.[45] Only 56% of APC patients were free of Fontan-failure after 25 years of follow-up.[13, 49] It is expected that in contemporary Fontan patients the incidences of heart failure and circulatory failure will be lower, however the exact numbers are generally lacking.

Studies in older APC Fontan patients show that 15-year freedom from supraventricular tachycardia ranges between 46-49%.[51] Since the introduction of the TCPC Fontan the incidence of arrhythmias has decreased.[51, 52] However after TCPC arrhythmias still remain prevalent, with freedom from tachyarrhythmias ranging between 81-94% 15 years after TCPC.[51] Studies have shown that ECC patients often experience less arrhythmic events, most likely explained by less atrial scarring when using this surgical technique.[49, 53, 54] However, follow-up duration often differs in studies comparing outcomes in patients with ILT versus ECC, complicating the comparison between the two techniques.[55, 56]

After the Fontan operation cardiac reinterventions, both surgical and by catheter, are relatively common.[13, 57] Like arrhythmias, cardiac reinterventions are more prevalent in the older Fontan cohorts compared to the younger cohorts operated with more contemporary techniques.[13, 58] Another complication in Fontan patients is PLE, with an incidence of 1.5-11%.[55] The cause of PLE is incompletely understood. Some studies suggest that elevated systemic venous pressure is related to the pathophysiology, although not all patients with PLE experience this. This suggests that more mechanisms are involved in the development of PLE.[55]

In conclusion, despite improvements in survival, adverse events occur frequently in Fontan patients during long-term follow-up. Fifteen years after contemporary Fontan completion the overall event-free survival ranges between 39-59%.[49, 59] This emphasizes the need for lifelong close follow-up in a specialized facility for these patients.[9] Research is necessary to determine the optimal TCPC technique in Fontan patients and to determine which other factors affect and/or predict long-term outcome and morbidity.

Figure 3. Tetralogy of Fallot



Tetralogy of Fallot

TOF is the most prevalent cyanotic ConHD, with a reported incidence of 0.34 per 1000 live births.[1] In the Netherlands, yearly approximately 60 babies with TOF are born.[4, 16] The tetrad was first described in 1673 by Nicolaus Steno, but was more extensively described by the French physician Etienne Fallot in 1888.[14, 60] TOF consist of four cardiac anomalies: a ventricular septal defect (VSD), a (sub) pulmonary stenosis (PS), an overriding of the aorta across the VSD and RV hypertrophy (Figure 3).[14, 60]

In chapter 6 of this thesis an extensive overview is given on the surgical treatment options and outcomes of TOF patients.

Tetralogy of Fallot repair

Before the surgical era, approximately 50% of TOF patients died within the first year of life.[61] In 1944 the first palliative procedure was performed by Helen Taussig, Alfred Blalock and Vivien Thomas. A connection was created between the subclavian artery and pulmonary artery to guarantee adequate pulmonary blood flow.[62] A decade later in 1954 the first intracardiac TOF repair was performed by Walter Lillehei.[63] Via a large right ventriculotomy the VSD wat closed and a large transannular patch (TP) was created to relieve the right ventricular outflow tract (RVOT) obstruction and PS.[63] In the first reported series, early mortality was as high as 40%,[63] but this decreased in the following decades with advances in surgical techniques and postoperative management.[14, 60]

Nowadays, TOF is often diagnosed prenatally or soon after birth.[14] Patients will be usually operated on between 3-6 months of age and surgery is performed using a transatrial-transpulmonary approach, avoiding a right ventriculotomy which is associated with RV scarring, arrhythmias and RV dysfunction.[61] Despite a successful TOF-repair the surgical relief of the PS often creates an incompetent pulmonary valve which causes pulmonary regurgitation (PR).[14]

Long-term outcome

Nowadays the reported early mortality is 1.1%, and 25-year survival rates between 93-97% have been described.[64-66] However, despite relatively good long-term survival, morbidity after contemporary TOF-repair remains high. Patients suffer from PR, RV dilatation, impaired RV and LV function, residual RVOT obstruction, arrhythmias and even sudden cardiac death.[61, 67, 68] PR is a key factor in the development of these problems and severe PR is often treated with a pulmonary valve replacement (PVR), although survival benefit of PVR has not been demonstrated.[9, 68-71]

Adverse events are common during follow-up in TOF patients. In an older surgical cohort the overall event-free survival was 25% after 40 years of follow-up, the freedom from reinterventions was 56% after 35 year follow-up.[72] In a contemporary cohort of patients with trans-atrial transpulmonary TOF-repair, 25-year freedom from reoperation was 75%.[64] The known predictors for adverse outcome in TOF patients have often been assessed in older surgical cohorts from a different surgical era.[67, 72, 73] As mentioned, many factors in surgical and postoperative management have changed over time, possibly influencing long-term outcome. It is therefore important to continuously follow contemporary TOF patients and to describe their long-term follow-up and assess factors associated with their long-term outcome.

In clinical practice, parameters are needed to identify ConHD patients at risk for future cardiac events or deterioration of cardiac function. Modalities to assess clinical condition in ConHD patients are echocardiography, cardiovascular magnetic resonance imaging (CMR), cardiopulmonary exercise test (CPET) and blood marker assessment. These modalities will be discussed in the remainder of this introduction.

Echocardiography

In clinical practice, echocardiography is widely used to assess cardiac function in ConHD patients.[74] Echocardiography is widely available, portable and relatively cheap.[75] However, imaging patients with a higher body mass or imaging the RV can be challenging due to a limited echo window.

In addition, the complex anatomy of univentricular hearts and multiple thoracotomies, which affects echocardiographic windows and image quality, potentially limits the use of echocardiography in a substantial proportion of patients.

Speckle tracking echocardiography (STE) is a technique which received increasing attention in the last two decades. STE is based on B-mode frame-by-frame tracking of acoustic markers (or speckles) throughout the cardiac cycle.[76, 77] This allows to assess

the degree and speed of cardiac deformation throughout the cardiac cycle (e.g. strain and strain rate).[77] In TOF patients a diminished LV global longitudinal strain is associated with cardiac death and severe arrhythmias.[78] In Fontan patients diminished global circumferential strain, measured by echocardiography, has been related to death or cardiac transplant during follow-up.[79] However echocardiographic longitudinal strain did not predict the presence of a low ejection fraction (EF) by CMR.[80]

Cardiovascular magnetic resonance imaging

Another imaging technique is CMR. CMR provides information on cardiac and extracardiac anatomy, valvular function and ventricular size, all without ionizing radiation.[81] CMR is the golden standard for measuring ventricular size and global function.[75, 82, 83] Subsequently CMR has an important place in the clinical follow-up and decision making in ConHD patients including TOF and Fontan patients.[9, 81] CMR has some limitations including relatively high costs, long scanning time, the need for anesthesia in younger patients and it is not always feasible in patients with cardiac devices or claustrophobia.[75]

In addition to assessing ventricular size and function, CMR techniques such as late gadolinium enhancement and T1 mapping are useful to detect fibrosis in the myocardium.[84] Myocardial fibrosis has been associated with arrhythmias, morbidity and mortality.[85] A relatively new and promising CMR technique is four dimensional (4D) flow. This technique visualizes blood flow and energy distribution in the heart and the great vessels.[86] The potential value of this technique in clinical practice has to be determined, but 4D flow derived energy loss and vorticity have been related to VO_2 max in Fontan patients.[87] CMR derived parameters such as end diastolic volume (EDV), cardiac mass and EF have been associated with long-term outcomes in some ConHD.[78, 88-90] However serial longitudinal CMR studies have been generally lacking as have CMR studies with longitudinal follow-up in more contemporary TOF and Fontan cohorts.

Stress CMR

Another potential clinically valuable CMR technique is stress CMR. This technique combines the gold standard for volumetric analysis with functional information during stress, providing potential information regarding early dysfunction.[91]

A stress CMR can be performed with physical stress and pharmacological stress.[92] In case of a physical stress CMR, a CMR compatible ergometer has to be used.[92] Physical stress creates activation of the cardiac, vascular and muscular system.[91] However several difficulties arise with physical stress; increased respiratory rate complicates breath-holding during the image acquisition and the maximal exercise is dependent on the patients motivation.[92] These practical issues have limited the use of physical stress imaging in clinical practice.[92] Pharmacological stress is more widely used. The most commonly used form of pharmacologic stress is intravenous dobutamine administration, a synthetic catecholamine that has a positive inotropic effect.[93] It increases the myocardial demand for oxygen in a comparable manner as physical

exercise. In children with heart diseases good clinical tolerance for low-dose dobutamine (7.5 µg/kg/min) stress imaging has been reported.[94]

In healthy volunteers a similar response to physical stress and dobutamine stress has been observed,[95] this response consists of a decrease in end systolic volume (ESV) and a subsequent increase of EF, while EDV does not change. In ConHD patients the ventricular response to stress is often abnormal: patients display an impaired increase in EF, and impaired decrease of ESV and an abnormal decrease in EDV.[96-100] In systemic RV patients with a biventricular circulation, an abnormal stress response was predictive for cardiac events during follow-up.[101] In Fontan and TOF patients, the relationship between abnormal stress response and subsequent outcome remains the subject of study.[102]

Cardiopulmonary exercise testing

Like cardiac imaging, a CPET is a recommended instrument in the follow-up of ConHD patients.[9] Patients with ConHD can experience a diminished exercise capacity and are often less active and exercise less vigorously than their healthy peers.[103-106]

A CPET is used to objectify exercise capacity.[9] During the CPET the patient wears a mask to measure the air volumes passing through the mask and to measure the inhaled oxygen and exhaled carbon dioxide.[107] These measurements allow to assess several CPET parameters such as oxygen consumption (VO_2), carbon dioxide production (VCO_2) and the respiratory exchange ratio (RER).[107] During the CPET also heartrate, peak workload, blood pressure and saturation are measured. The peak VO_2 (maximal reached VO_2) is the primary outcome of the CPET. Peak VO_2 is corrected for the weight of the patient and is also calculated as percent of predicted peak VO_2, using reference data of healthy volunteers.

Like other ConHD patients, Fontan and TOF patients often experience diminished exercise capacity and a reduced peak VO_2.[108, 106, 109] Several clinical parameters have been associated with CPET parameters.[108-113] Fontan patients operated on with older surgical techniques experience a lower peak VO_2 compared to patients operated on with contemporary TCPC techniques.[109] Furthermore, patients with a RV morphology display a more rapid decline in exercise capacity over time.[110] A poor clinical outcome has been associated with exercise capacity in both Fontan and TOF patients.[106, 109, 114-117] In TOF patients a peak VO_2 of ≤15.5 ml/kg/min or a peak VO_2 ≤65% of predicted are associated with hospitalization for sustained ventricular tachycardia and death during subsequent follow-up.[115, 118] Likewise, a study in Fontan patients observed that a peak VO_2 of ≤16.6 ml/kg/min was associated with new morbidity and death.[117]

Serum biomarkers

In ConHD patients pathways related to inflammation, hypertrophy, remodelling and fibrosis are most likely involved in the development of heart failure and decline in cardiac function.[119] These pathways have been the subject of extensive research in acquired heart disease, but remain less well understood in ConHD.[85, 119] However the

search continues to unravel these mechanisms and to search for biomarkers of these processes. A biomarker is "*any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease*".[120] Potentially, assessment of blood biomarker levels is a relatively non-invasive method to monitor the clinical condition of ConHD patients and to identify those patients at risk for clinical deterioration or adverse events.

In the last decades neurohormones such as brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) have received much attention.[121] The ventricular myocyte releases NT-proBNP as a response to stretch and in acquired heart failure patients NT-proBNP levels have an important role in the clinical follow-up.[122, 123] In TOF and Fontan patients (NT-pro)BNP levels have been related to the clinical condition.[88, 98, 124, 125] Although NT-proBNP levels are often within normal range in Fontan patients,[126] Fontan patients with heart failure, Fontan patients operated on using older techniques and Fontan patients with morphological RV's have higher NT-proBNP levels.[124, 127-129] The role of NT-pro BNP in clinical practice in cyanotic heart disease has been fully established.

In the recent years several other serum biomarkers have been identified in ConHD patients such as galectin-3, suppression of tumorigenicity 2 (ST2) and growth differentiation factor 15 (GDF-15). Galectin-3 is involved in several biological processes including fibrosis and inflammation.[130, 131] In a large adult ConHD cohort an increased galactin-3 was observed in 7% of the patients and a higher galactin-3 was associated with adverse cardiovascular events.[132] In adult Fontan patients, elevated galectin-3 is associated with adverse outcome.[133] In a pediatric cohort undergoing ConHD surgery, elevated galectin-3 levels were associated with an increased risk of mortality and readmissions, as did ST2.[134, 135]

ST2 is a protein which can be expressed in a soluble form (sST2) and a transmembrane form (ST2 ligand), it is it marker for fibrosis and myocardial apoptosis.[136] ConHD patients display higher levels of sST2 compared to healthy volunteers, also different sST2 levels are observed between different ConHD types.[136] In adult complex ConHD sST2 is a predictor for all-cause mortality and adverse events.[136 137] Also in children with ConHD and heart failure, sST2 was significantly correlated with fractional shortening and left ventricular end systolic and end diastolic dimensions.[138]

Like sST2, GDF-15 is a marker of abnormal function, in pediatric Fontan patients higher GDF-15 levels are related to impaired echocardiographic singe ventricle EF.[139] GDF-15 is a member of the transforming growth factor beta (TGFβ) family and is a marker of oxidative stress.[140-143] In adult ConHD patients, higher GDF-15 levels correlate with poorer functional status, cardiac dysfunction and adverse outcome.[141, 142, 144] Specifically in Fontan patients higher GDF-15 levels are associated with impaired systolic function.[139]

Additional studies are necessary to unravel the biochemical mechanisms of heart failure in ConHD patients and to find new biomarkers and potentially find targets for therapy.

Aims and outline of this thesis

The studies in this thesis are part of the multicenter prospective study entitled: 'COBRA^3: **Co**ngenital heart defects: **B**ridging the gap between Growth, Maturation, **R**egeneration, **A**daptation, late **A**ttrition and **A**geing'. The multicenter prospective COBRA^3 study has several objectives:

1. To assess factors during mid-term to long-term follow-up which are related to the achievement of myocardial homeostasis or are related to deterioration of clinical state and impending failure.
2. To assess the impact of ConHD on the growth, homeostasis and premature ageing of the heart, particularly for the RV.
3. To carry out prospective and cross-sectional assessment of parameters of cardiac function and maintenance of myocardial homeostasis in ConHD patients.

This thesis focuses on describing the mid- to long-term outcomes of Fontan and TOF patients and to assess parameters which correlate with endpoints or adverse outcome.

Part I – Fontan circulation

Part I of this thesis focuses on the Fontan circulation. In **chapter 2** an overview is given on the surgical treatment options, management and outcomes of the Fontan circulation. In **chapter 3** we investigate in a retrospective follow-up study, whether differences exist in long-term outcomes in TCPC patients operated on with the ILT vs the ECC technique and current modifications of these techniques. In **chapter 4** we look into the ventricular response to dobutamine stress CMR of Fontan patients and if this is related to outcomes during follow-up. In **chapter 5** biomarkers, CMRs and CPET's were assessed in a multicenter prospective study to evaluate if these factors are associated with outcome in a young and contemporary Fontan cohort.

Part II – Tetralogy of Fallot

The second part of this thesis focus on TOF patients. **Chapter 6** starts with a review on the current treatment strategies, the management and long-term outcomes of TOF patients. **Chapter 7 and 8** describe a retrospective follow-up study in transatrial transpulmonary operated TOF patients. These studies research surgical determinants of long-term outcome and whether there is an optimal timing for primary TOF repair. **Chapter 9** assesses whether the ventricular response to dobutamine stress CMR is related to outcome in TOF patients. In **chapter 10** we assess the research question of biomarkers, CMR and CPET's are associated with cardiac function and long-term outcome in young Fontan patients. We will discuss the findings of all the studies in **chapter 11**, the General Discussion of this thesis.

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Part I

Fontan circulation

Chapter 2

State of the art of the Fontan strategy for treatment of univentricular heart disease

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Abstract

In patients with a functionally univentricular heart the Fontan strategy achieves separation of the systemic and pulmonary circulation and reduction of ventricular volume overload. Contemporary modifications of surgical techniques have significantly improved survival. However, the resulting Fontan physiology is associated with high morbidity.

In this review we discuss the state of the art of the Fontan strategy by assessing survival and risk factors for mortality. Complications of the Fontan circulation, such as cardiac arrhythmia, thrombo-embolism and protein-losing enteropathy are discussed. Common surgical and catheter-based interventions following Fontan completion are outlined. We describe functional status measurements such as quality of life and developmental outcomes in the contemporary Fontan patient. The current role of drug therapy in the Fontan patient is explored. Furthermore, we assess the current use and outcomes of mechanical circulatory support in the Fontan circulation and novel surgical innovations.

Despite large improvements in outcomes for contemporary Fontan patients, a large burden of disease exists in this patient population. Continued efforts to improve outcomes are warranted. Several remaining challenges in the Fontan field are outlined.

Introduction

Functionally univentricular congenital heart disease (CHD), in which only one ventricle is fully developed, poses a complex clinical problem. Estimates of the incidence of this disease entity range from 0.08 to 0.4 per 1000 births.[1-3] Functionally univentricular CHD entails different morphological diagnoses, the most common of which are: hypoplastic left heart syndrome (HLHS) (25% to 67% of functionally univentricular hearts), tricuspid atresia (15% to 24%), and double inlet left ventricle (14% to 18%).[1, 3-5] It is estimated that currently there are about 22.000 patients in Europe and approximately 50.000 in the United States.[6] Recent advancements in prenatal screening have increased the rates of prenatal diagnosis and possibly termination of pregnancy in patients with univentricular hearts.[1, 7] Despite the low incidence, improvements in treatment have reduced the mortality to the point where a large number of patients survives into adulthood.

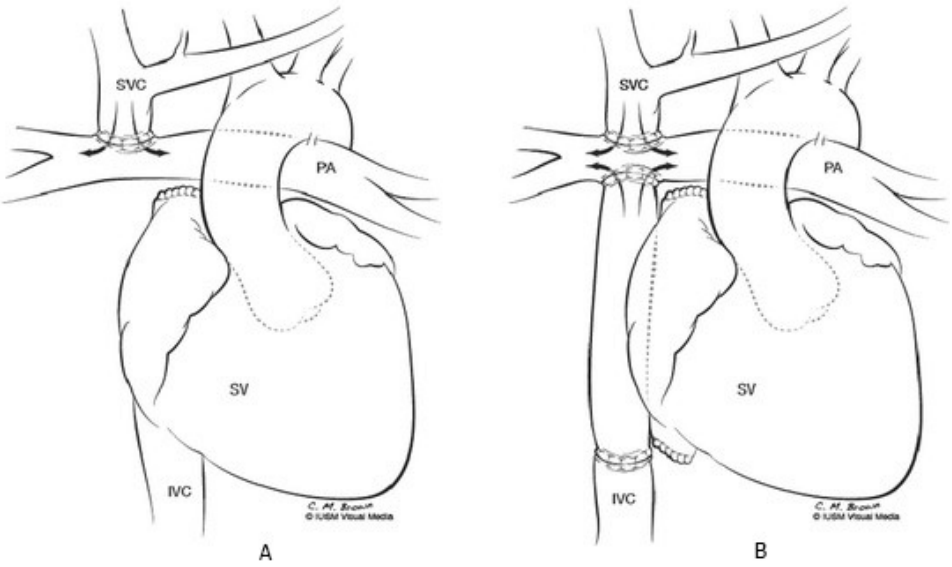
Palliation can be achieved with the Fontan strategy. A series of operations is performed to palliate the adverse effects of a univentricular heart. The Fontan strategy refers to the landmark surgery for tricuspid atresia by Fontan et al.[8] In the 'early days' of these procedure it was attempted to replace the function of the right ventricle with the right atrium by connecting the right atrium to the pulmonary artery. Although short-term results were unprecedented, this strategy caused dilation of the right atrium, resulting in arrhythmia and thrombo-embolism due to sluggish blood flow.[9] Modifications of this surgery are referred to as atrio-pulmonary connections (APC). In a later era, de Leval et al. found atrial contractions did not contribute significant power to the APC circuit, and proposed the intra-atrial lateral tunnel (ILT), a trans-atrial connection using an intra-atrial baffle connecting the inferior caval vein to the pulmonary artery in a more energetically favorable manner. Currently, most centers employ an extra-cardiac conduit (ECC), a prosthetic conduit that bypasses the atrium completely. Both ILT and ECC are referred to as total cavo-pulmonary connection (TCPC) Fontan modifications.

A Fontan circuit was originally created in a single surgical setting. This resulted in relatively high mortality. A staged TCPC, in which a series of operations is performed at different ages, is the current standard of care. These operations are tailored to the individual anatomy of the patient. First, the single ventricle (SV) needs to be connected to the aorta, which may require extensive surgery, such as the Norwood procedure for HLHS. At approximately 3 to 6 months of age, a partial cavo-pulmonary connection (PCPC), connecting the superior caval vein to the pulmonary artery, i.e. bidirectional Glenn procedure, is performed. Completion of the TCPC is usually performed between 18 months and 4 years of age.[4] The connections and circulatory pattern after these operations are illustrated in Figure 1.

These patients require a lifetime of highly specialized care and significant healthcare resources. In Oceania, the mean hospital costs across all stages of palliation are approximately $200.000 per patient.[10] Following Fontan palliation, hospital admission

rates for patients are 8 times higher than the general population[11] and both length of stay and hospital costs are higher compared to other CHD diagnoses, including e.g. Tetralogy of Fallot.[12-14]

Figure 1. Illustration of the anatomic relations following PCPC **(A)** and TCPC **(B)** palliation.



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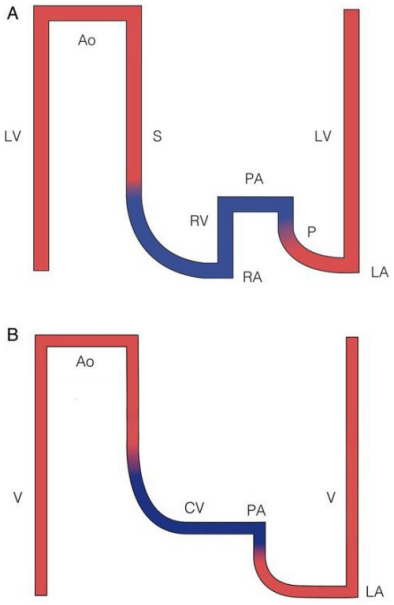
Abbreviations: IVC: Inferior vena cava; SVC: superior vena cava; PA: pulmonary artery; SV: Single ventricle.

Physiology

In unpalliated univentricular CHD cyanosis occurs due to mixing of saturated and unsaturated blood in the heart. The SV is also exposed to volume overload as it drains both systemic and pulmonary venous return at the same time. The Fontan strategy reduces volume overload and restores normoxaemia. Following PCPC surgery some volume unloading of the single ventricle is achieved. Following TCPC the volume load of the SV is further reduced.[15] Furthermore, after TCPC the systemic and pulmonary blood flows are connected in series, rather than parallel as before this strategy has been deployed. This comes at the expense of the lack of a ventricle supplying energy to the pulmonary circulation. This is illustrated in Figure 2. The single ventricle provides the energy needed to attain blood flow through the systemic as well as the pulmonary vascular bed and is subjected to increased afterload. After TCPC central venous pressures are higher than normal. Pulsatility in the pulmonary artery is mostly lost and there is preload insufficiency of the single ventricle. This highly abnormal circulation is called the Fontan circulation. The resulting physiology has been referred to as a

Figure 2. Scheme of pressures in the normal circulation **(A)** and the Fontan circulation **(B)**.



This figure has been reproduced from Gewillig et al. with permission of the author.[158]

This scheme illustrates the effects of the lack of a prepulmonary pump in the Fontan physiology. Red represents oxygenated blood where blue represents deoxygenated blood.
Abbreviations: LV: Left ventricle; Ao: aorta; S: systemic circulation; RA: Right atrium; RV: Right ventricle; PA: Pulmonary artery; P: Pulmonary circulation; LA: Left atrium; V: Single ventricle; CV: Caval veins.

"Fontan paradox", where systemic venous pressure is high in the presence of relative pulmonary artery hypotension.[16] This might augment lymphatic outflow, and impede lymphatic inflow from the thoracic duct. Several complications of the Fontan strategy have been linked to abnormalities in lymphatic drainage. Because of the multiple inherent hemodynamic challenges of the Fontan circulation, it is generally considered a palliative procedure.[17]

The aim of this paper is to provide an overview of current outcomes, treatment options and remaining challenges to improve outlook for patients with univentricular heart disease.

State of the Art

Overall survival

Survival following the Fontan procedure has increased dramatically in the past decades. We will discuss data from recently published reports of large cohorts with long follow-up intervals. An overview of studies assessing survival is presented in Figure 3, obtained from Kverneland et al.[18]

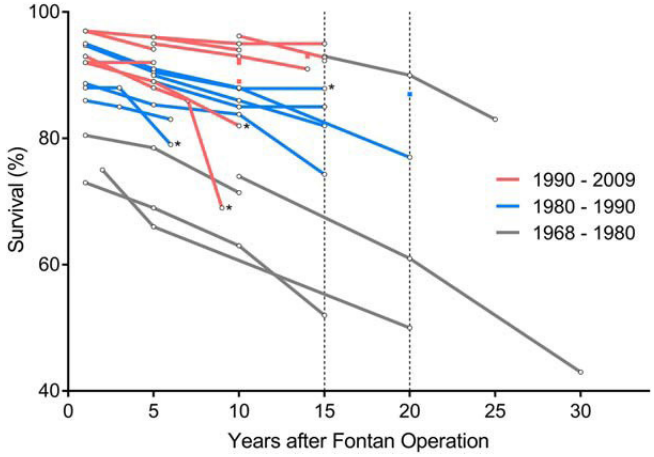
In a recent study from Oceania perioperative mortality decreased from 8% between 1975 and 1990 to 1% in 2001-2010. [19] In this cohort early Fontan takedown occurred in 2% of patients. 10-Year survival among patients discharged with a Fontan circulation was 89% following APC and 97% for both ECC and ILT.[20] Survival at 25 years was 76%. This group was comprised only of APC patients.

In a retrospective study from the Mayo clinic of 40 years and 1052 Fontan patients, overall survival was 74% at 10 years, 61% at 20 years and 43% at 30 years.[21] Survival was significantly higher in later surgical eras, with a 10-year survival of 95% for patients operated after 2001. Interestingly, patients operated with the ECC technique showed better overall survival over ILT. It should be taken into account that ILT patients suffered from diagnoses with worse prognosis.

A Danish national registry described outcomes for SV patients from 1977 to 2009.[1] 50% of patients died before Fontan completion. Overall survival improved in later birth eras. Five-year survival for any univentricular CHD increased from 22% in 1977-1989 to 51% in 2000-2009.

One should note that follow-up studies after Fontan procedures reflect results of an earlier surgical era and do not necessarily represent the outlook of patients treated according to the current standard of care.

Figure 3. Survival following Fontan completion.



This figure has been reproduced from Kverneland et al. with permission of the author.[18]

Each line represents a study assessing survival at multiple time points and is colored by surgical era. Dots represent Kaplan-Meier survival estimates. Studies marked * show survival curves for death, transplant or Fontan revision, others show survival curves for only death.

Determinants of survival

Several factors have been associated with survival after the Fontan procedure. Of pre-operative factors, male gender[20] and specific CHD diagnosis, most strikingly for hypoplastic left heart syndrome (HLHS)[22], have been associated with worse long-term survival. Perioperative risk factors for mortality include APC type procedure, earlier surgical era, older age at procedure, concomitant valve replacement and prolonged post-operative pleural effusion.[22] Postoperative factors that affect survival include: elevated central venous pressure and lower arterial saturation[23]; imaging derived parameters such as lower global longitudinal strain on echocardiography and higher end-diastolic volume measured by magnetic resonance imaging (MRI)[22]; peak heart rate and peak oxygen uptake during cardiopulmonary exercise testing[22, 24, 25]; serum levels of sodium, creatinine, and brain natriuretic peptide.[22, 26, 27]

Cardiac complications

Although survival following Fontan completion has increased over time, the Fontan strategy has been associated with important morbidity, most likely related to extensive surgical procedures and the highly abnormal circulatory state after these procedures. In recent cohorts event-free survival has ranged from 59% to 81 % at 15 years.[20, 28]

The most commonly reported event is cardiac arrhythmia. Supraventricular tachycardia (SVT) contributes significantly to late mortality in Fontan patients.[29] SVT has been associated with Fontan type, with highest risk for APC type, followed by ILT and lowest for ECC.[20, 30] Results may have improved for the ILT technique after introduction of the prosthetic modification.[31] The incidence of SVT increases during follow-up and after 20 years of follow-up 10% to 60% of patients has experienced some form of SVT.[31, 32]

Failure of the Fontan circulation can occur even in longstanding uncomplicated Fontan circulations. The definition of Fontan failure varies but generally includes either excessive constitutional limitations of the Fontan physiology, abnormal parameters of hemodynamic function, poor functional status or the presence of Fontan sequelae.[33] Fontan failure occurs in 2-13% of patients, depending on definitions and follow-up period.[33] A 56% 25-year freedom of Fontan failure for APC connections has been reported.[20]

Extracardiac complications

Abnormalities of Coagulation. Blood flow can be slow in the Fontan circuit due to the absence of a prepulmonary pump. This promotes coagulation. Furthermore, coagulation factor abnormalities have been described in the SV patient, even before PCPC palliation.[34] Thrombo-embolic events are more common following APC surgery than TCPC.[34] The prevalence of thrombi is particularly high in those that develop atrial arrhythmias.[35] Up to 65% of thrombi are detected within the first year following TCPC (early thrombo-embolic events).[36] Early thrombo-embolic events probably relate to perioperative factors, such as ECMO use and altered hemodynamics. Beyond 10 years

after Fontan completion incidence of late thrombo-embolism steadily increases.[36] Reports of the incidence of thrombo-embolism are complicated by different definitions and methods of detection. Studies report incidences of late thrombo-embolism between 1% and 25%.[28, 37] Silent thrombi are detected with transesophageal echocardiography in up to 33% of patients.[38] Thrombo-embolic events have been reported to account for 8% of Fontan deaths.[39]

Liver function abnormalities, cirrhosis and even hepatocellular carcinoma have been reported following Fontan surgery.[40] The elevated systemic venous pressures encountered in the Fontan circulation leads to chronic venous congestion in the liver. However, the exact mechanism for Fontan-associated liver disease remains unknown, as does how best to monitor progression.[41, 42] The American College of Cardiology have recently provided a position statement on the subject, advising laboratory and imaging screening at least every 3-5 years in children and at least every 1-3 years in adult Fontan patients.[43] Preventive strategies need to be developed.

Protein-losing enteropathy (PLE) is a devastating complication of the Fontan circulation where loss of protein in the gastro-intestinal tract occurs, leading to low albumin levels, edema, pleural effusions and ascites. Incidences have been reported between 3% and 29%.[21, 28, 32, 44] It is thought to be caused, in part, by impairments in the lymphatic drainage. Hepatoduodenal lymphatic connections exist in some patients as a normal anatomic variant, which might induce competition in lymphatic flow in the presence of elevated venous pressure, diverting lymphatic flow to the gastro-intestinal tract.

Plastic bronchitis is a serious pulmonary complication of the Fontan circulation, in which large gelatinous casts are formed in the airways. It is thought to be related to abnormal lymphatic drainage directly into the airways, resulting in cast formation. Reported incidences range from 0.5% to 4%.[45-47]

Chronic kidney disease is estimated to be present in up to 50% of adult Fontan patients and is associated with adverse outcomes.[27, 48] With the increasing availability of cystatin C determined GFR, a muscle mass independent estimate, the prevalence of clinically significant renal dysfunction appears to be lower.[49] GFR estimates based on serum creatinine concentrations probably overestimate renal function in Fontan patients.[48]

Psychological, psychiatric and cognitive defects have been described in Fontan patients. Cerebral MRI has shown morphological differences in some cerebral structures of Fontan patients compared with healthy controls.[50, 51] Interestingly, the pituitary gland, supplied by a portal venous system similar to the liver, appears to be enlarged following Fontan surgery.[52] The relevance of this possible congestion on the endocrine system remains unclear.

Re-interventions

Many patients require additional surgical and catheter-based interventions following Fontan completion. 20 year freedom of re-operation following TCPC procedures in

recent eras ranges from 86% to 92%.[53] In older cohorts higher re-operation rates have been reported.[21, 54, 55] The most common surgical re-intervention procedures, in order of incidence, are pacemaker implantation in 9% to 23% of patients,[20, 21] Fontan revision or conversion in 3% to 18% of patients[9, 21, 56] and atrioventricular (AV) valve repair in 1% to 14% of patients.[21, 56, 57]

Fontan conversion, from APC to TCPC, can improve functional status and exercise tolerance in the failing Fontan circulation.[58] AV valve repair after Fontan completion is considered in patients with moderate to severe regurgitation, but survival following successful repair remains inferior to that of patients without prior AV-regurgitation.[59, 60]

For several reasons re-interventions by catheter may be required. A fenestration in the atrial tunnel, inducing a right-to-left atrial shunt, can be created during surgery to decrease systemic venous pressure, increase ventricular preload, and improve cardiac output at the cost of lower arterial saturation. This fenestration sometimes closes spontaneously or can be closed via catheter at a later time.[61]

Hemodynamically significant obstruction in the Fontan pathway may occur, most commonly in the left pulmonary artery.[54, 62] In the absence of a pre-pulmonary pump, this can severely affect the Fontan circulation, and obstructions are routinely dilated or stented. Systemic to pulmonary venous collaterals can produce a right-to-left shunting which often worsens in time. Coiling of these collaterals is routinely performed in some centers, although no survival benefit has been demonstrated.[63]

Aorto-pulmonary collaterals are common in the Fontan circulation. They increase pulmonary blood flow but induce a volume overload on the single ventricle and might increase pulmonary artery pressure, limiting flow from the caval veins.[62] During exercise, aortopulmonary flow increases, possibly augmenting loading conditions of the ventricle.[64] A large aorto-pulmonary collateral burden has been associated with worse short-term outcomes.[65] No clear consensus regarding the long-term effects and management of these collaterals exist.[62]

Catheter ablation of an arrhythmogenic substrate is common. Long term success rates vary between 15% and 72%.[66, 67] The reported incidence of catheter-based interventions, i.e. excluding diagnostic cardiac catheterization without intervention, varies heavily with 3% to 65% of patients requiring at least one additional catheter intervention following Fontan completion.[28, 53, 54, 56, 68] The most common catheter interventions are fenestration closure (10% to 64% of patients with a fenestration require catheter-based fenestration closing[53, 54, 56, 69]), occlusion of veno-venous or aorto-pulmonary collaterals (incidence 10% to 20%)[54, 56] and stenting and dilation of (all types of) obstructions in the Fontan pathway (incidence 6% to 19%).[54, 56, 70]

Other outcomes and functional status

Most studies report a diminished quality of life in Fontan patients compared to healthy controls.[71-75] Physical and emotional functioning are the most severely affected domains.[71, 76] Low perceived health status can lead to unnecessary restrictions in daily

life. Furthermore, increased rates of developmental disorders and lower intelligence scores have been reported in the Fontan population.[50, 73]

Fontan patients have a moderately decreased exercise capacity compared to healthy controls.[77] Mean peak oxygen uptake ranges from 61% to 74% of predicted values.[77-79] A small fraction of Fontan patients have normal exercise capacity.[80] Exercise capacity in the Fontan patient has been shown to decrease over time.[78, 79] Exercise capacity is predictive of hospital admissions, quality of life and late mortality.[22, 25, 76, 79] Exercise training can be done successfully in Fontan patients and can improve quality of life, functional class and health perception in a short-term follow-up.[81-84] Whether exercise training has a role in optimizing long-term outcome is currently not clear.[81, 83-86] Resistance training can be used to increase muscle mass. In the Fontan patient this could augment peripheral venous return, augment ventricular preload and improve cardiac output.[87] Similarly, a benefit of inspiratory muscle training has been demonstrated.[88]

Despite high morbidity and suboptimal outcomes, most patients with a well-functioning Fontan circulation manage to lead fulfilling lives, are employed, may attain academic achievements, can participate in sports and are able to successfully carry pregnancy to term.[89-91]

Assessment techniques

Fontan patients are routinely assessed for health and functional status. Diagnostic cardiac catheterization has been standard practice in the pre-TCPC evaluation as it provides excellent anatomic and necessary hemodynamic information regarding the pulmonary artery pressure, pulmonary vascular resistance, and end-diastolic single ventricle pressure.[92] There is recent interest in omitting cardiac catheterization in the pre-TCPC assessment for low risk SV patients.[92-94] No consensus regarding this policy has been reached, as long-term outcomes are currently unavailable. Catheter-based interventions are discussed above.

Cardiac magnetic resonance imaging (CMR) is routinely performed during follow-up after TCPC, particularly to assess ventricular size and function and to quantify large vessel flow including the amount of collateral flow.[95-99] Death and (being listed for) heart transplantation have been associated with higher indexed end diastolic volume (>125 ml/m^2) as assessed with CMR in adolescents with a Fontan circulation.[100, 101] Combined with a computational fluid dynamics approach, CMR might provide very useful information on the Fontan circulation and can aid in the evaluation of modifications in treatment strategies.[102]

Echocardiographic strain measurements have been shown to predict survival in the Fontan population and predict length of hospital stay following TCPC.[101, 103] Assessment of VA coupling may be another important parameter as it is independent of the, often impaired, ventricular load. VA coupling has been shown to be suboptimal in some Fontan populations.[104] Currently, VA coupling has not been associated with long-term outcomes in the Fontan population.

Lymphangiography could play an important role in the management of Fontan complications with a suspected lymphatic pathogenesis, such as PLE and plastic bronchitis. In patients suffering from PLE or plastic bronchitis increased diameters of major lymphatic vessels have been noted.[105] Abnormal lymphatic depositions in the lungs and liver have been visualized in patients suffering from plastic bronchitis and PLE, respectively.[106, 107]

Medical therapy

Anticoagulation, in the form of anti-platelet drugs or vitamin K antagonists (VKA), is commonly indicated considering the increases risk for thrombo-embolic events, as discussed above in the '*extracardiac complications*' section.[108] A meta-analysis by Alsaied et al. showed both acetylsalicylic acid and VKA were equally effective in preventing thrombo-embolic complications.[109] However, if INR is not properly controlled outcomes on VKA are worse compared to acetylsalicylic acid.[110] Novel oral anticoagulants (NOACs) do not require frequent monitoring and have mostly outperformed VKA in the adult population. Thirty day outcomes following NOAC initiation show no major adverse events in the adult CHD population.[111] However, no NOAC agent currently has FDA approval for use in children.

Medical prevention of circulatory failure in the Fontan circulation

Various medications have been assessed in the management of Fontan failure.
No studies have shown benefit of ACE inhibitor therapy on survival, ventricular function or cardiopulmonary exercise outcomes.[112, 113]

Vasodilator drugs have been used to lower pulmonary vascular resistance.[114, 115] Sildenafil has increased ventricular function, exercise capacity and NYHA status after 6 weeks of follow-up.[116, 117] The effects of bosentan, an endothelin antagonist, in the Fontan population have varied.[118-123] No long-term survival benefit of vasodilator therapy has yet been demonstrated.[116]

Mechanical circulatory support for the failing Fontan circulation

The failing Fontan circulation can be supported by mechanical assist devices. Despite increasing use and the development of novel devices specifically for the pediatric and CHD population, experience in this population is still limited.[124] Mechanical support devices are mostly used as a bridge to transplant in the failing Fontan.[125] Recent reports showed a 60% 12-month survival in 48 Fontan patients with a ventricular assist device, proving viability of longer mechanical circulatory support.[126, 127] A total biventricular artificial heart, the SynCardia, has been used to bridge a failing Fontan patient to transplant.[128] A registry of mechanical circulatory support specifically for SV patients has been initiated.[129] Currently, mechanical circulatory support in Fontan patients is associated with worse survival compared to mechanical circulatory support patients with a biventricular circulation.[130-132]

Cardiac transplantation

Cardiac transplantation is the only treatment that truly corrects Fontan physiology, and it is employed in the failing Fontan circulation. In large cohorts 1.6% to 3.6% of patients ultimately underwent cardiac transplant.[20, 21] Survival following cardiac transplantation in Fontan patients is generally worse compared to other types of CHD.[133, 134] Five-year survival ranges from 60% to 67%.[133-135]

Surgical innovations

Continuous efforts are made to improve the surgical techniques used in Fontan surgery. Recently, a Y-shaped graft has been proposed for the connection of the inferior vena cava to the left and right pulmonary artery.[136] Theoretically, this graft is more energetically favorable and provides better distribution of hepatic blood flow between the left and right pulmonary artery, distributing 'hepatic factors' that may prevent formation of intrapulmonary collaterals, more equally. Worse energetic performance and pulmonary flow distributions in comparison to ECC connections have been noticed in practice.[137, 138]

Fontan completion without cardiopulmonary bypass, particularly with the ECC technique, is an attractive option. However, experience is still limited and reported rates of conduit replacement and outcomes following off-pump procedures differ across centers.[139-142]

Less invasive surgical approaches such as lateral thoracotomy have been described in this population.[143] Hybrid procedures, which combine trans-catheter and surgical approaches, have been implemented in the initial management of HLHS.[144] Long term outcomes are favorable and some centers have adopted this hybrid approach as the standard for selected patient populations.[145]

Remaining challenges

A contemporary Fontan strategy uses either the ILT or ECC modification. Two large meta-analyses have recently compared surgical strategies and found no differences in early or late mortality and Fontan takedown between ECC and ILT.[30, 146] Theoretical advantages of both techniques have been discussed extensively in literature.[147, 148] Further research should assess contemporary differences in outcomes between modifications and help guide the preferred procedure for future Fontan patients. This may include alternative concepts, like the Y-graft or combinations with external energy supply (pumps).

Remodeling of the SV, which is exposed to volume overload at birth and is volume deprived following TCPC procedure, is not understood very well. A better understanding of mechanisms of remodeling during these stages and the interaction of ventricular size and function with the Fontan baffle function, pulmonary circulation, atrial function and ventriculo-arterial (VA) interaction is required to find better means to preserve cardiac function. The search for new targets for drugs that may help to preserve cardiac and circulatory function continues.

Some controversy regarding the timing of TCPC surgery exists. Proponents of early TCPC argue a prolonged period of volume overload leads to adverse cardiac remodeling and reduced cardiac function.[149] Others argue the Fontan circulation inherently leads to complications, and surgery should be delayed to reduce the amount of time in Fontan physiology.[150] Other factors to be considered are the technique used, with ILT allowing TCPC at lower body weight than ECC, since small sized conduits (< 18 mm) need to be avoided.[148, 151] Studies assessing the optimal timing of ECC procedures are currently being performed.

The effect of systemic to pulmonary venous and aorto-pulmonary collaterals on the Fontan circulation remains poorly understood. These collaterals could provide some benefit in patients with a suboptimal Fontan circuit. How these collaterals develop and why some patients seem more prone to this development remains to be determined. Increasing our understanding of the role of collaterals could help guide selection of patients who will benefit from intervention. This requires well-designed (multicenter) studies. Several treatment modalities of PLE have been described in small series, including catheter-based strategies of both blood and lymphatic vessels and surgical re-implantation of the innominate vein into the common atrium.[152-156] More comprehensive analysis is needed to determine the efficacy and safety of these procedures.

Drug therapy has been shown to be able to decrease pulmonary vascular resistance in the short-term, making this a promising therapy for the Fontan patient. However, currently no long-term benefit has been demonstrated. The role of drug therapy in the Fontan circulation needs to be studied more extensively.

These questions require answers to make better informed decisions in the management of these challenging patients, suffering from some of the most severe kinds of CHD. We have an opportunity to help this growing patient population not just to survive, but thrive and live full, satisfying lives.

Conclusion

The modern Fontan strategy has significantly transformed outcomes for patients with univentricular CHD. This has led to a large and growing population of Fontan patients surviving into adulthood. However, morbidity remains high and increases as this population ages and grows in proportion. Efforts to reduce morbidity and improve quality of life in these patients are ongoing. These efforts are focused on improving surgical techniques, developing novel diagnostic and therapeutic tools and increasing our understanding of the highly abnormal Fontan physiology.

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Chapter 3

Staged total cavopulmonary connection: serial comparison of intra-atrial lateral tunnel and extracardiac conduit taking account of current surgical adaptations

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Abstract

Objectives
To compare the outcome of the intra-atrial lateral tunnel (ILT) and the extracardiac conduit (ECC) techniques for staged total cavopulmonary connection (TCPC). To compare the current modifications of the TCPC technique, the prosthetic ILT technique with the current ECC technique with a ≥ 18-mm conduit.

Methods
We included patients that had undergone staged TCPC between 1988 and 2008. Records were reviewed for patient demographics, operative details and events during follow-up (death, surgical and catheter-based reinterventions and arrhythmias).

Results
Of the 208 patients included, 103 were ILT (51 baffle, 52 prosthetic) and 105 were ECC patients. Median follow-up duration was 13.2 years (interquartile range 9.5-16.3). At 15 years after TCPC, overall survival was comparable (81% ILT vs 89% ECC, p=0.122). Freedom from late surgical and catheter-based reintervention was higher for ILT than for ECC (63% vs 44%, p=0.016). However, freedom from late arrhythmia was lower for ILT than for ECC (71% vs 85%, p=0.034). In a subgroup of patients with an current TCPC technique, we compared use of prosthetic ILT with ≥ 18-mm ECC, we found no differences in freedom from late arrhythmias (82% vs 86%, p=0.64) and freedom from late reinterventions (70% vs 52%, p=0.14).

Conclusions
A comparison between the updated prosthetic ILT and current ≥ 18-mm ECC techniques revealed no differences in late-arrhythmia-free survival or late reintervention-free survival. Overall, outcomes after staged TCPC are relatively good and reinterventions occurred more frequently in the ECC group, while late arrhythmias were more common in the ILT group.

Introduction

The Fontan operation is the procedure of choice in patients in whom biventricular repair is not feasible.[1, 2] Over the past 30 years, two main Fontan techniques have been developed. The intra-atrial lateral tunnel (ILT) technique, originally used the right atrial wall (all or part of it) to create a baffle to tunnel the blood from the inferior vena cava directly to the pulmonary arteries.[3-5] When combined with a connection of the superior vena cava to the pulmonary arteries, this resulted in the total cavopulmonary connection (TCPC).[1] Subsequently, the extracardiac conduit (ECC) technique was described, which uses a conduit from the inferior vena cava to the pulmonary arteries.[6] Over time, the atrial baffle ILT technique has evolved into the prosthetic ILT, in which the intra-atrial tunnel is created using part of a prosthetic tube rather than part of the atrial wall.[7]

Because of haemodynamic advantages and a significant improvement in operative outcomes, the single-stage TCPC has been replaced by a staged approach,[8] which has resulted in relatively low late mortality rates.[9, 10] However, a direct comparison of the long-term outcomes of the two TCPC techniques remains difficult due to the limited number of patient-years and due to differences between duration of follow-up after the two TCPC techniques. Furthermore, the ILT and ECC techniques have been updated over time, which further limits up-to-date information on the outcomes of current approaches.[11]

Remarkably, a serial follow-up of TCPC patients has hardly been done. Without this data, and without data on outcome and survival after application of the updated current TCPC techniques, surgeons lack confirmation that these techniques continue to be equally effective in terms of outcome and survival. To address this lack of data, we made use of a previously described cohort of staged ILT or ECC patients in the Netherlands.[12] The updated serial analysis of this cohort had two objectives: first, to compare the staged ILT and ECC techniques in terms of outcome and event-free survival after a longer follow-up period and second, to compare outcome in patients who have undergone TCPC procedures that use the updated ILT or ECC techniques, i.e. to compare the current prosthetic ILT with the current ECC using a large-diameter conduit.

Methods

Patients

We included all patients who were part of the previously published analysis and who had therefore undergone completion of a staged TCPC with the ILT or ECC technique between January 1988 and January 2008. The inclusion and exclusion criteria were published previously.[12] The study complies with the regulations of institutional review boards with regard to retrospective data collection. The local ethics committees approved the retrospective study and waived informed consent.

Definitions

The medical records of all patients were reviewed up until September 2017. We recorded all cardiac events during follow-up until the patient's last visit to the outpatient clinic. The primary endpoint was death; secondary endpoints were defined as thromboembolism (TE) that required intervention and/or hospitalization, protein-losing enteropathy (PLE), plastic bronchitis, arrhythmias, late reoperations or reinterventions. Arrhythmias were defined as documented bradyarrhythmias or tachyarrhythmias that required intervention and/or hospitalization.

Early complications and mortality were defined as occurring within 30 days after TCPC or before hospital discharge, all other sequelae were considered late. We note that in the previous analysis we used a different definition of early mortality; the current definition is that of the Society of Thoracic Surgeons Congenital Heart Surgery Database.[12, 13]

Statistical analysis

Continuous variables with a normal distribution (according to the Shapiro-Wilk test) were expressed as mean and standard deviation (SD). Variables with a non-normal distribution were presented as median and interquartile range (IQR). Differences between groups were analysed by Student's t-tests or with Mann-Whitney U tests. Categorical variables were presented as numbers and percentages and were evaluated by Chi-square test or the Fisher's exact test.

The incidences of the primary and secondary endpoints over time were evaluated with the Kaplan-Meier method. Differences in the incidence of endpoints between the TCPC types were evaluated using the Log-Rank test. Cox proportional hazard analysis was used to determine whether parameters had an influence on the probability of the event. We found no deviations of the proportional hazards assumption by inspecting the plots of log minus log survival functions. A p-value <0.05 was required for a parameter to remain in the multivariable model. All analyses were performed using the SPSS statistical software package version 24.0 (IBM Corp. in Armonk, NY, USA). Two-sided p-values <0.05 were considered statistically significant.

Results

A total of 208 patients were included. Patient and surgical characteristics are shown in Table 1. Hypoplastic left heart syndrome (HLHS) was more common in the ECC group and there was a trend towards more heterotaxy syndrome patients in the ILT group (Table 1). Further details regarding the patient characteristics have been published previously.[12]

In this cohort, the first staged ILT was performed in 1990, and the first staged ECC was performed in 1996. In the patients who underwent ILT, a baffle ILT was used in 51 patients and a prosthetic ILT in 52 patients. In the patients who underwent ECC, the

Table 1. Patient and surgical characteristics

	ILT (n=103)	ECC (n=105)	P-value
Males (n, %)	63 (61)	55 (52)	0.20
Ventricular morphology			
Left (n, %)	53 (52)	61 (41)	0.56
Right (n, %)	48 (47)	43 (41)	
Tricuspid atresia (n, %)	16 (16)	38 (36)	0.001
HLHS (n, %)	15 (15)	29 (28)	0.021
Heterotaxy syndrome (n, %)	13 (13)	6 (6)	0.084
Pre-Fontan procedures	231	267	
Modified BT shunt (n, %)	34 (33)	18 (17)	0.008
Central shunt (n, %)	6 (6)	17 (16)	0.017
Pulmonary banding (n, %)	26 (25)	23 (22)	0.57
Atrioseptectomy (n, %)	12 (12)	5 (5)	0.070
Norwood (BT-shunt/ RV-PA conduit) (n, %)	15 (11/4) (15)	32 (25/7) (30)	0.006
Systemic AVV repair (n, %)	2 (2)	3 (3)	1.00
Branch pulmonary artery repair (n, %)	19 (18)	25 (24)	0.34
CoA repair (n, %)	13 (13)	30 (29)	0.005
Age at BDG (years)	0.9 (0.6–1.6)	0.7 (0.5–1.3)	0.002
Interval between BDG and TCPC (years)	1.8 (1.3–2.4)	2.2 (1.7–3.0)	<0.001
Age at TCPC (years)	3.0 (2.4–3.8)	3.2 (2.5–4.2)	0.35
Weight at TCPC (kg)	14.0 (12.1–15.9)	14.0 (12.2–15.9)	0.99
CPB time (minutes)	105 (90–105)	141 (96–202)	0.001
Minimal temperature (°C)	28 (26–29)	30 (28–32)	<0.001
ICU stay (days)	6 (3–12)	4 (2–7)	<0.001
Fenestration	19 (18.4)	14 (13.3)	0.31

Results are given as median (IQR) or counts (percentages).

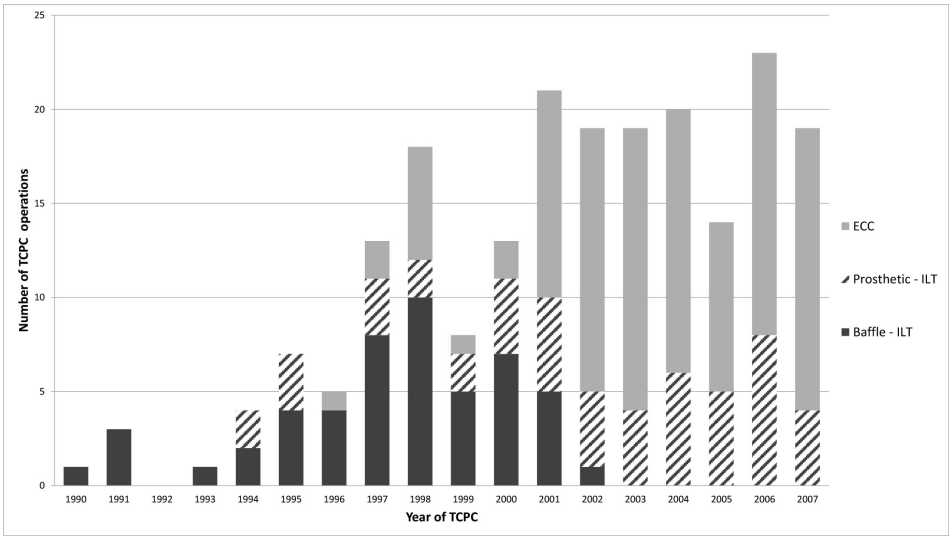
Abbreviations: AOV: aortic valve, AVV: atrioventricular valve, BDG: bidirectional Glenn anastomosis, BT: Blalock-Taussig, CoA: aortic coarctation, CPB: cardiopulmonary bypass, ECC: extracardiac conduit, HLHS: hypoplastic left heart syndrome, ICU: intensive care unit, ILT: intra-atrial lateral tunnel, PA: pulmonary artery, PM: pacemaker, RV: right ventricle, TCPC: total cavopulmonary connection.

size of the conduit diameter varied, as did the graft material. One patient received a 16-mm Gore-Tex conduit and 17 patients received a 16-mm Vascutek conduit, 33 patients received an 18-mm Gore-Tex conduit and 56 patients received a Gore-Tex conduit with a diameter that was at least 20 mm. Figure 1 shows the change over time in the surgeons' preferences for the different staged TCPC techniques.

The total analysis consisted of 2467 patient-years (1315 ILT, 1152 ECC). The median follow-up duration since TCPC was 13.2 (9.5–16.3) years. The median follow-up

durations of the ILT and ECC patients were 15.3 (10.2–18.7) and 12.0 (9.3–14.5) years, p<0.001. A total of nine patients were lost to follow-up; we verified that seven of these patients were still alive at the end of the follow-up and included them in the analysis for mortality. For the remainder of the analyses, these nine patients were censored at the time of their last outpatient clinic visit.

Figure 1. Staged TCPC over time



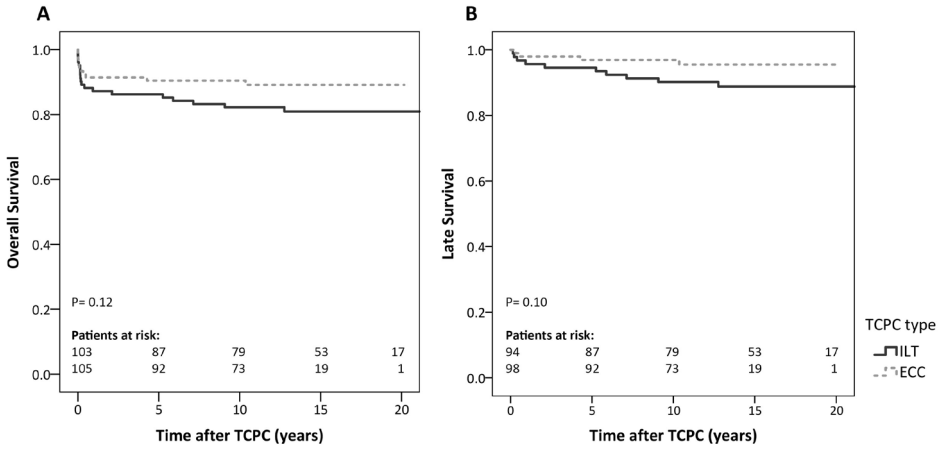
Abbreviations: ECC: extracardiac conduit, ILT: intra-atrial lateral tunnel, TCPC: total cavopulmonary connection.

Mortality

Overall mortality was 14% (19 ILT, 11 ECC). Kaplan-Meier estimates for overall survival after ILT were 82% at 10 years (standard error (SE) 4%), and 81% 15 years (SE 4%); after ECC they were 91% at 10 years (SE 3%), and 89% at 15 years (SE 3%) (p=0.12) (Figure 2). For the entire cohort, overall survival at 15 years was 85% (SE 3%). Multivariable analysis revealed the following independent predictors for overall mortality: cardiopulmonary bypass time (CPB), right ventricle (RV) morphology and the duration of intensive care unit (ICU) stay after TCPC (Table 2).

Late mortality occurred in 10 ILT and 4 ECC patients, after a median of 38.3 (4.5–91.4) months after TCPC. Causes for late death were Fontan failure in five, sudden cardiac death in three, sepsis and multiple organ failure in one, ventricular fibrillation in one, thrombus in the systemic RV in one, bradycardia during surgical closure of the fenestration in one, and endocarditis in one patient; in one patient the cause of death was unknown. Kaplan-Meier estimates for late survival after ILT were 90% at 10 years

Figure 2. **(A)** Overall and **(B)** late survival after TCPC



Abbreviations: ECC: extracardiac conduit, ILT: intra-atrial lateral tunnel, TCPC: total cavopulmonary connection.

(SE 3%), and 89% at 15 years (SE 3%); after ECC they were 97% at 10 years (SE 2%), and 96% 15 years (SE 2%) (p=0.10) (Figure 2). Dominant RV was the only predictor in univariable analysis for late mortality (HR: 3.61; 95% CI 1.13–11.53, p=0.030).

Although no patients underwent Fontan takedown or heart transplantation, one patient was listed for heart transplantation.

Late reinterventions

After TCPC, 140 late reinterventions (surgical and catheter-based) were performed in 84 patients. Late surgical reinterventions accounted for 53 (38%) of all late reinterventions, with 35 patients needing two or more late reinterventions. Table 3 shows the types of reinterventions performed after TCPC. In ten patients, the ECC conduit was replaced. All of these patients had originally received a 16-mm conduit: one was a Gore-Tex conduit and the other nine were Vascutek conduits which are no longer in use.[14]

ILT patients had better Kaplan-Meier estimates for late reintervention-free survival (Figure 3): 75% at 10 years (SE 5%), and 63% at 15 years (SE 6%); for ECC, estimates were 54% at 10 years (SE 5%), and 44% at 15 years (SE 6%) (p=0.016). Univariable analysis showed that patients were significantly more likely to require late reinterventions if they had an ECC (HR: 1.73; 95% CI 1.10–2.71, p=0.021) or HLHS (HR: 2.06; 95% CI 1.25–3.39, p=0.005). In multivariable analysis, both the ECC technique and HLHS remained independent predictors for late reinterventions during follow-up (HR: 1.64; 95% CI 1.04–2.58, p=0.032 and HR: 1.93; 95% CI 1.17–3.20, p=0.010).

Late arrhythmias

Late arrhythmias occurred in 41 patients (20%) after a median period of 9.9 (5.6–12.4) years after TCPC. Bradyarrhythmia was present in 15 patients, and tachyarrhythmia occurred in 22 patients, one of whom died of ventricular fibrillation. Four patients

Table 2. Predictors for overall mortality and late arrhythmias

	Hazard ratio	95% CI	P-value
Overall mortality: univariable			
Males	1.81	0.83–4.00	0.14
ILT Fontan	1.78	0.85–3.75	0.13
Age at Fontan (years)	0.92	0.76–1.12	0.41
RV morphology	3.16	1.45–6.90	0.004
HLHS	1.67	0.76–3.65	0.20
Heterotaxy syndrome	2.11	0.81–5.50	0.13
Pre-Fontan AVV regurgitation	1.30	0.62–2.72	0.50
CPB time (minutes)	1.01	1.00–1.01	0.002
ICU stay after TCPC (days)	1.04	1.02–1.06	<0.001
Overall mortality: multivariable			
RV morphology	2.31	1.02–5.22	0.044
CPB time	1.004	1.00–1.01	0.012
ICU stay after TCPC (days)	1.03	1.02–1.06	<0.001
	Hazard ratio	**95% CI**	**P-value**
Late arrhythmias: univariable			
Males	1.18	0.63–2.21	0.63
Baffle ILT	2.65	1.41–4.99	0.003
Age at TCPC (years)	1.00	0.90–1.11	0.97
RV morphology	1.64	0.86–3.11	0.13
HLHS	1.27	0.55–2.90	0.58
Heterotaxy syndrome	0.75	0.23–2.43	0.63
Number of post-TCPC procedures*	1.59	1.18–2.12	0.002
Pre-Fontan AVV regurgitation	1.01	0.54–1.89	0.99
CPB time (minutes)	1.00	0.99–1.00	0.97
ICU stay after TCPC (days)	1.02	1.00–1.05	0.055
Late arrhythmias: multivariable			
Baffle ILT	2.65	1.41 - 4.99	0.003
Number of post-TCPC procedures*	1.60	1.18 - 2.17	0.003

*Excluding pacemaker procedures

Abbreviations: AVV: atrioventricular valve, CPB: cardiopulmonary bypass, ECC: extracardiac conduit, HLHS: hypoplastic left heart syndrome, ICU: intensive care unit, ILT: intra-atrial lateral tunnel, RV: right ventricle, TCPC: total cavopulmonary connection.

Table 3. Late reinterventions after TCPC

	ILT (n= 94)	ECC (n= 98)	P-value
Patients with reinterventions (n, %)	37 (39)	47 (48)	0.23
Time between TCPC and first reintervention (years)	7.2 (3.3–12.1)	4.7 (2.5–8.7)	0.079
Number of surgical reinterventions (n, %)	26 (28)	27 (28)	0.99
Number of percutaneous reinterventions (n, %)	22 (23)	31 (32)	0.20
Fenestration closure (n, %)	9 (10)	6 (6)	0.37
Pulmonary artery intervention (n, %)	3 (3)	13 (13)	0.017
Coiling collaterals (n, %)	10 (11)	17 (17)	0.18
PM implantation (n, %)	15 (16)	5 (5)	0.017
PM battery replacement (n, %)	3 (3)	4 (4)	1.00
AVV repair (n, %)	1 (1)	4 (4)	0.37
AOV repair/mechanical AOV implantation (n, %)	7 (7)	7 (7)	0.94
ECC replacement (n, %)		10 (10)	
Other (n, %)	12 (13)	7 (7)	0.19

Results are given as median (IQR or counts (percentage

Abbreviations: AOV: aortic valve, AVV: atrioventricular valve, CPB: cardiopulmonary bypass, ECC: extracardiac conduit, ILT: intra-atrial lateral tunnel, PM: pacemaker, TCPC: total cavopulmonary connection.

suffered an out-of-hospital cardiac arrest (three deaths, one survivor with subsequent ICD for secondary prevention) and were suspected of ventricular tachyarrhythmia (no documentation of heart rhythm related to cardiac arrest was available).

Freedom from late arrhythmias was better in ECC patients than in ILT patients (p=0.034, see Figure 3). Univariable analysis showed that patients were significantly more likely to experience arrhythmia if they had undergone the baffle ILT technique (HR: 2.65; 95% CI 1.41–4.97, p=0.003) or if they had a higher number of post-TCPC procedures (excluding pacemaker procedures; HR: 1.57; 95% CI 1.17–2.11, p=0.003. In multivariable analysis, the baffle ILT technique and the number of post-TCPC interventions remained independent predictors for late arrhythmias during follow-up (Table 2).

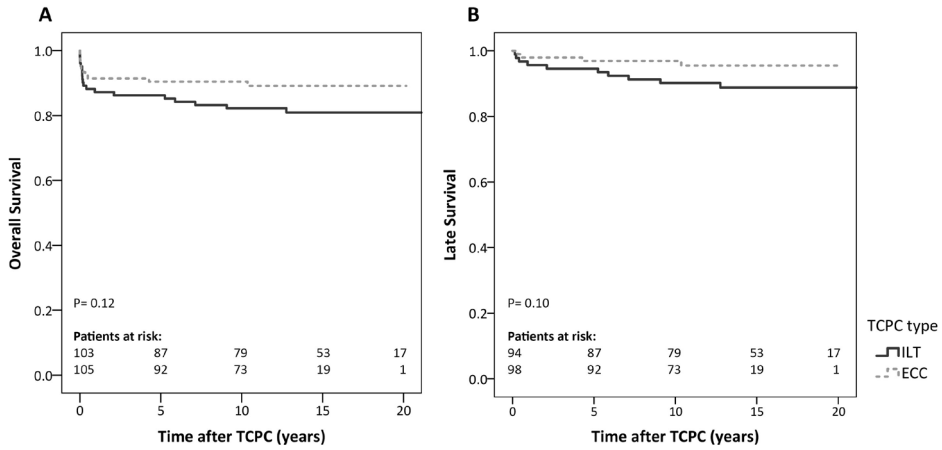
Other events

Other complications were relatively rare: PLE occurred in a total of nine patients, two in the ILT group and seven in the ECC group, after a median period of 6.6 (2.8–9.4) years after TCPC; plastic bronchitis was identified in four patients, two ILT and two ECC.

Thromboembolic events (TEs) occurred in 13 patients (6 ECC and 7 ILT): two patients had deep venous thrombosis; two patients had a thrombus in the left pulmonary artery; one patient had a pulmonary embolism; one patient had a transient ischemic attack; one patient had a thrombus in the systemic RV; one patient developed a thrombus on a mechanical aortic valve while not taking anticoagulation; two patients had chest pain with focal delayed enhancement on MRI; and two patients had a cerebral infarction.

No difference in event-free survival between the ILT and ECC groups were found (p=0.35). At 10-year follow-up, the freedom from any event for all patients was 53% (SE 4%); for ILT this was 59% (SE 5%) and for ECC 46% (SE 5%). At 15 years, freedom from any event for all patients was 39% (SE 4%).

Figure 3. (A) Late reintervention-free survival and **(B)** late arrhythmia-free survival after TCPC



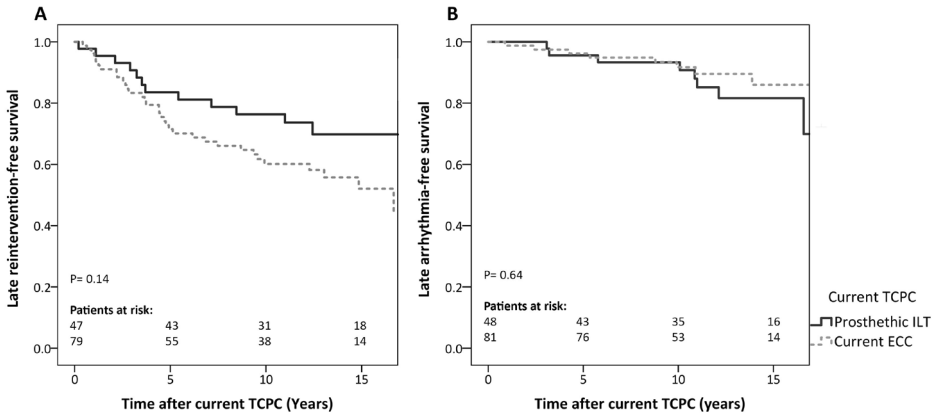
Abbreviations: ECC: extracardiac conduit, ILT: intra-atrial lateral tunnel, TCPC: total cavopulmonary connection.

Current TCPC techniques

Since their introduction, both TPCP techniques have been adapted and updated, and this was reflected in the patients in our study: 52 ILT patients had received a prosthetic ILT, and 89 ECC patients had received a conduit with a diameter ≥18 mm. We considered these two subgroups of patients as having being treated with "current TCPC" techniques. The median follow-up duration of the prosthetic ILT and ≥18-mm ECC patients was similar (12.5 (9.4–15.9) years vs 11.0 (9.3–14.5) years, p=0.12). For all patients treated with current TCPC techniques, the median follow-up duration post TCPC was 11.6 (9.3–14.9) years.

The occurrence of late arrhythmias was more frequent in the older baffle ILT group than in the prosthetic ILT group (21 (72%) vs 8 (28%), p=0.004). Late arrhythmia-free survival did not differ between the prosthetic ILT and ≥18-mm ECC group (p=0.64, see Figure 4). There were also no differences in late reintervention-free survival between the prosthetic ILT and ≥18-mm ECC groups (p=0.14, see Figure 4). Neither were differences observed in overall survival (p=0.36) or event-free survival (p=0.58) between the prosthetic ILT and ≥18-mm ECC groups.

Figure 4. **(A)** Reintervention-free survival and **(B)** arrhythmia-free survival late after current TCPC



Abbreviations: ILT: intra-atrial lateral tunnel, ECC: extracardiac conduit, TCPC: total cavopulmonary connection.

Discussion

The results of this study indicate that for the prosthetic ILT technique and the ≥18-mm ECC technique currently in use, patients experience no differences in late arrhythmia-free survival and late reintervention-free survival. The two groups of patients in this study had a comparable median follow-up duration of approximately 12 years.

The long-term follow-up of Fontan patients has been studied extensively. However, many previous studies have included not only TCPC but also older Fontan techniques.[9, 15] In studies that have included TCPC techniques only, a direct comparison of long-term outcomes after the different TCPC procedures is limited by the differences in the duration of follow-up between the ILT and ECC techniques. This difference has been caused by the shift over time towards a preference for the ECC procedure, resulting in relatively higher numbers of older ILT patients.[11]

Survival

Late survival after TCPC was 94% at 10 and 92% at 15 years. Our figures for late mortality are somewhat lower than the 97% late survival at 10 years post TCPC in a recently published large cohort.[9] An explanation for this difference could be that their patients were relatively older at TPCP, namely 3.8 years for ILT and 4.8 years for ECC, which may point towards different selection criteria for eligibility for TCPC than those used in our cohort. In a recent study by Downing *et al*.[10] the median age at TCPC was lower, namely 2.3 years, with an overall survival of 92% at 10 years and 88% at 15 years post TCPC. For patients who survived the first year after TCPC, their survival was similar to that reported here.

We observed a trend towards better survival for ECC patients. Two recent meta-analyses have shown a similar trend.[11, 16] However, such a trend was not apparent in the current TCPC modifications in our cohort: patients with a prosthetic ILT and ECC patients with a conduit ≥18 mm.

A potential benefit of the ECC is that it gives surgeons the option of performing the TCPC with a shorter CPB time, or even off-pump.[16, 17] However, in our study, ILT patients had a significantly shorter median CPB time. In our study, both the ILT technique and the surgical centre were associated with CPB time. Our multivariable models for overall mortality identified CPB time, duration of ICU stay and RV morphology, as independent predictors.

Late reinterventions

Despite relatively good survival, morbidity remains high in Fontan patients.[9, 18, 19] In our cohort, ILT patients had a better freedom from late reinterventions, which was mainly caused by the ECC patients who required replacement of a 16-mm Vascutek conduit. These conduits are no longer in use.[14] Pulmonary artery reinterventions were also more common in the ECC group.

Importantly, comparison of the currently used ECC technique (excluding 16-mm conduits) and the currently used prosthetic ILT technique showed no difference in reintervention-free survival after a medium-term follow-up of similar duration. Internationally available guidelines indicate that reintervention can be considered in selected patients in case of obstruction of systemic or pulmonary venous return, exercise limitation, or unexplained exercise deterioration and fatigue. However, such guidelines rarely provide quantitative limits.[20, 21] As a result, different centres may have different thresholds for reinterventions, and this could have influenced our observations.

Late arrhythmias

Compared with older Fontan cohorts, the burden of arrhythmias is relatively low in our contemporary TCPC population.[19] It has been suggested that ECC is the preferred technique because, theoretically, it minimizes factors that may lead to arrhythmias.[17] In a recent large Fontan study, the incidence of late atrial tachycardia was 7% for ILT and 2% for ECC patients ($p<0.001$). However, follow-up duration differed between both techniques, 9.2 years for ILT and 4.7 years for ECC, $p<0.001$).[22] In our analysis, we found that late arrhythmia-free survival was better in prosthetic ILT patients than in baffle ILT patients. This was also observed in a recent cross-sectional prospective study conducted by our group.[7] A key finding of our study is that we observed no differences in late arrhythmia-free survival after TCPC between patients who had undergone the current prosthetic ILT technique and those who had undergone the current ECC technique, in a cohort in which the two groups had a similar duration of medium-term follow-up.

Other late events

Despite relatively low late mortality, we observed a high number of events, particularly surgical and catheter-based reinterventions. Fifteen-year event-free survival was 39%, with no difference between the entire cohort of ILT and ECC patients. In the Australian-New Zealand cohort that included both TCPC and APC patients, freedom from adverse events at 15 years was 59%.[9] This is somewhat better than the percentage found here and is most likely explained by the use of different definitions for adverse events and event-free survival. Clearly not all events have the same impact, demonstrating that improved consensus on outcome measures is required.[23]

Theoretically, ECC patients are more prone to develop thromboembolism.[1] Most of our patients were on platelet-aggregation inhibitors or vitamin K antagonists. We observed no differences in the rate of thromboembolism between ILT and ECC patients. However, the most severe cases – a thrombus in the systemic chamber, and a sub-total and total occlusion of the left pulmonary artery, conduit and chamber – occurred in ECC patients.

Several other studies have also reported finding no differences in incidence of thromboembolism between ILT and ECC patients.[24, 25] The incidence of thromboembolism in our cohort was lower than that reported in most other studies and this might be explained by differences in the methods used to identify thromboembolism.[26]

Study limitations

This is a retrospective study, although the number of patient-years is comparable there are more older ILT patients. Another limitation is that our data only cover a follow-up period of 15 years. Future research is therefore required to determine whether the slight outcome differences between the ILT and ECC at the current follow-up duration are still present after a longer duration of follow-up.

Conclusions

Key findings were the similar rates of late arrhythmia-free survival and late reintervention-free survival in patients undergoing TCPC using the current prosthetic ILT modification and the current ECC technique that uses conduits with a diameter of at least 18 mm. In the entire cohort, no differences were observed in overall or late mortality between the ILT and ECC groups. Although survival is relatively good after staged TCPC, overall event-free survival at 15 years was 39%.

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Chapter 4

Ventricular response to dobutamine stress CMR is a predictor for outcome in Fontan patients

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Abstract

Objectives
To evaluate the prognostic value of dobutamine stress CMR in Fontan patients.

Background
The Fontan circulation has serious long-term complications. Evaluation of ventricular function using exercise or pharmacological stress cardiac magnetic resonance imaging (CMR) has been advocated as tool to reveal impending Fontan dysfunction. Several studies have shown that patients with a Fontan circulation have an abnormal (dobutamine) stress response.

Methods
Fontan patients who received low dose dobutamine stress CMR were followed prospectively. Cardiac events were recorded, time-to-event analyses (Kaplan-Meier method) and Cox proportional hazard regression analyses were performed to determine the predictive value of dobutamine stress CMR for the composite study endpoint including cardiac death, cardiac reintervention, hospitalization or cardioversion/ablation for arrhythmias.

Results
92 patients, median age 11.5 (9.8 – 15.3) years, median time after Fontan completion 8.0 (6.9 – 11.3) years underwent a baseline stress CMR. Overall indexed end systolic volume (39 ± 16 vs 26 ± 13 ml/m^2, p<0.001) and indexed end diastolic volume (85 ± 21 vs 73 ± 21 ml/m^2, p<0.001) decreased during stress. Ejection fraction (EF) increased during stress CMR (55 ± 10 vs 65 ± 10%, p<0.001). 23 patients reached the study endpoint, 3.1 (1.5 – 5.7) years after baseline CMR. They had a lower increase in EF during stress (functional reserve (FR)) compared to the non-event-group (6 ± 7 vs 11 ± 6 %, p=0.002). Patients with a FR of ≥ 14% (highest quartile) had significantly less events during follow-up. Patient who reached the study endpoint also had a higher ventricular mass; 73 ± 23 vs 57 ± 16 gram/m^2, p<0.001. Multivariable analyses identified FR (HR 0.86/%; 95% CI 0.79 – 0.93; p<0.001) and indexed ventricular mass (HR 1.04/gram/m^2; 95% CI 1.02 – 1.07; p=0.001) as predictors of the study endpoint.

Conclusion
Ventricular response to dobutamine stress is a predictor for events in young patients with a Fontan circulation.

Introduction

The Fontan has evolved over the years into the treatment of choice in most patients with a functional univentricular heart.[1] Univentricular hearts account for approximately 9% of all congenital heart defects.[2] Since the development and evolution of the Fontan procedure long-term survival of these patients has improved, resulting in an increasing number of surviving Fontan patients.[3]

Despite decline of mortality and morbidity after the Fontan operation over the last decades, long-term complications including circulatory failure, thromboembolic events, arrhythmias and death are still common.[3, 4] Morphological factors, e.g. hypoplastic left heart syndrome (HLHS) and functional measurements such as peak oxygen uptake (VO_2) and ventricular size and function have been found predictors for outcome.[5-9]

Cardiovascular magnetic resonance (CMR) imaging provides valuable information on anatomy and is the gold standard for measuring ventricular function in these patients.[10, 11]

Evaluation of ventricular function using exercise or pharmacological stress CMR has been advocated as additional tool to reveal impending dysfunction.[12, 13] Several studies have shown that patients with a Fontan circulation have an abnormal response to dobutamine or physical stress.[14-19]

However, the prognostic value of stress CMR in Fontan patients is still unclear. Our aim was to evaluate the value of dobutamine stress CMR to predict adverse outcome in patients with a Fontan circulation.

Methods

Patients and methods

We included patients that underwent a dobutamine stress CMR in the setting of two cross-sectional and prospective studies in five tertiary referral centers between 2004 and 2012. All participants, and if necessary their parents, gave written informed consent before inclusion in these studies. The inclusion and exclusion criteria, study protocol, methods, adverse event rate and results have been published previously.[10, 17] Patients included in the current analysis have been shown not to differ from other eligible patients with regard to age, gender, age at Fontan completion and surgical techniques.[10, 17]

The dobutamine CMR was considered as the baseline measurement. At this time, patients underwent CMR imaging at rest and during low-dose dobutamine stress, cardiopulmonary exercise testing (CPET) and assessment of N-terminal pro-brain natriuretic peptide (NT-proBNP). After the baseline examination patients received regular patient specific care in the outpatient clinic. For the purpose of the current study the last available medical data were reviewed for cardiac events during follow-up.

CMR acquisition

CMR imaging was performed with a dedicated phased-array cardiac surface coil. All images were acquired without breath-hold. Technical details of the sequences and the protocols have been previously published.[10, 17]

Scans were performed at rest and repeated during continuous infusion of dobutamine-hydrochloride (Centrafarm Services, Etten-Leur, the Netherlands) with a dosage of 7.5 μg/kg/min. Dobutamine infusion was decreased to 5.0 μg/kg/min (or if necessary stopped) when the heartrate increased >50%, when the systolic and/or diastolic blood pressure increased >50% or decreased <20%, when rhythm disturbances were seen, or with complaints of the patient. Details on our dobutamine stress protocol have been published previously.[10, 17]

CMR analysis

Analysis was performed with the software packages MASS and FLOW (Medis Medical Imaging Systems, Leiden, the Netherlands). Contours were manually drawn in end-diastole and end-systole, papillary muscle and trabeculae were excluded from the blood pool. All CMR's were analysed under supervision of one of the authors (WH) with longstanding experience.

End diastolic volume (EDV) and endsystolic volume (ESV) were obtained and used to calculate ejection fraction (EF). Ventricular volumes were defined as the sum of the volumes of the systemic ventricle and the hypoplastic chamber. All ventricular volumes were indexed (i) for body surface area (BSA).

A normal stress response to low dose dobutamine in healthy individuals consist of a decrease in ESVi and a subsequent increase of EF.[20] Therefore an abnormal response to stress was defined as the inability to decrease ESV during stress and/or the inability to increase EF during stress.

Changes in CMR parameters were calculated as follows: parameter change (Δ) = $parameter_{stress} - parameter_{rest}$, functional reserve (FR) is described as the $EF_{stress} - EF_{rest}$.

Clinical parameters

Blood samples were taken from a peripheral vein after 30 minutes rest in supine position. Plasma and serum were separated within 30 min after collection and stored at −80°C. NT-proBNP was measured with the Elecsys electrochemiluminescence immunoassay (Roche Diagnostics).

CPET were performed on a bicycle ergometer according to previously described protocols.[21, 22] From these exercise tests the VO_2 peak was assessed and expressed as percentage of predicted values. Exercise tests with a peak respiratory exchange rate (RER peak) of ≥1.0 were included in the analysis.[23]

Study endpoint

The study endpoint was described as cardiac death, out of hospital cardiac arrest (OHCA), cardiac reintervention, thromboembolic events, protein losing enteropathy (PLE), hospitalization for arrhythmias or cardioversion/ablation for arrhythmias.[6, 9, 24, 25]

Statistical methods

Continuous variables with a normal distribution were summarized as mean (SD). Differences between patients with and without events, between dominant ventricles and Fontan technique were analysed by Students t-tests. Variables with a non-normal distribution (according to the Shapiro-Wilk test) were presented as median (25-75th percentile) and between-group differences were analysed by Mann-Whitney U tests. Categorical variables were presented as numbers and percentages, whereas between-group differences were evaluated by Chi-square test or the Fisher's exact tests.

Differences between rest and stress CMR measurements were analysed with paired Students t-tests. The cumulative endpoint-free survival was estimated by the method of Kaplan-Meier curves and between-group differences were evaluated by the log-rank test. We applied Cox proportional hazard regression analyses to relate CMR findings with endpoint-free survival. A p-value <0.05 was required for the variable to be retained in the equation for multivariable cox regression models. Correlations between CMR parameters were studied by Pearson's correlation coefficients (r_p).

All analyses were performed using the SPSS statistical software package version 21.0 (SPSS, Inc., Chicago, IL, USA). Two-sided p-values <0.05 were considered statistically significant.

Results

All patients that had successfully undergone stress CMR for evaluation of a Fontan circulation were included. Dobutamine stress CMR was well tolerated in most patients. One patient reported a minor headache. In 15 patients dobutamine infusion was reduced to 5 µg/kg/min due to an increase of heartrate >50% or because of frequent ventricular extra systoles. These patients were included in the analysis. Adverse effects recovered spontaneously directly after terminating the dobutamine infusion.[10, 17]

A total of 92 patients were included in our analysis. These patients underwent stress CMR at a median age of 11.5 (9.8 – 15.3) years. Median time after Fontan completion was 8.0 (6.9 – 11.3) years, patients characteristics and clinical parameters at baseline are shown in Table 1.

At baseline 27 patients had more than mild AV (atrioventricular) valve regurgitation assessed by echocardiography (n=87) or CMR (n=5). Thirty-one (33.7%) patients had a dominant right ventricle (RV) and 56 (60.9%) patient had a dominant left ventricle (LV), in 5 (5.4%) patients the anatomy of the dominant ventricle was undefined. The intra-atrial tunnel (ILT) technique was used in 45 (48.9%) patients, 42 (45,7%) patients had an extracardiac conduit (ECC) and in 5 (5.4%) patients an atriopulmonary connection (APC) was used. There was no significant difference in age between patients with an ILT or ECC (11.9 (9.7 – 16.6) years vs 11.1 (10.2 – 13.4) years, p=0.28). Patients with dominant RV were younger at baseline compared to patients with dominant LV (10.3 (9.5 – 14.0) vs 11.8 years (10.2 – 15.5) p=0.04). Patients with an APC were older than patients with a TCPC, 19.4 (16.4 – 21.2) vs 11.3 (9.8 – 14.8) years, p=0.002.

Table 1. Patient characteristics at baseline visit

	Patients (n=92)	Patients with event[a] (n=23)	Patients without event[b] (n=69)	P-value[a, b]
Male (n, %)	58 (63.0)	17 (73.9)	41 (59.4)	0.212
Median age at baseline visit (years)	11.5 (9.8-15.3)	13.3 (10.2-16.0)	11.3 (9.7-15.0)	0.193
Median time after Fontan completion (years)	8.0 (6.9-11.3)	8.4 (6.8 - 12.2)	7.8 (6.9 - 10.8)	0.404
Dominant ventricle				
Right (n, %)	31 (33.7)	8 (34.8)	23 (33.3)	
Left (n, %)	56 (60.9)	13 (56.5)	43 (62.3)	
Undetermined (n, %)	5 (5.4)	2 (8.7)	3 (4.3)	
Median age at Fontan (years)	3.0 (2.5-3.9)	3.2 (2.5 - 4.2)	3.0 (2.5 - 3.8)	0.636
TCPC (n, %)	87 (94.6)	20 (87.0)	67 (97.1)	0.063
ECC (n, %)	42 (45.7)	7 (30.4)	35 (50.7)	0.146
ILT (n, %)	45 (48.9)	13 (56.5)	32 (46.4)	0.399
APC (n, %)	5 (5.4)	3 (13.0)	2 (2.9)	0.098

Results are given as mean (SD), median (25-75th percentile) or as counts (percentages).
Abbreviations; APC: atriopulmonary connection, ECC: extracardiac conduit, ILT: intra-atrial lateral tunnel, TCPC: total cavopulmonary connection.

Ventricular response to stress

The results of the CMR are shown in Table 2. For the entire group there was a significant decrease in ESVi (39 ± 16 vs 26 ± 13 ml/m^2, p<0.001) and in EDVi (85 ± 21 vs 73 ± 21 ml/m^2, p<0.001) during stress. Indexed stroke volume (SVi) did not change during stress, EF increased during dobutamine stress (55 ± 10 vs 65 ± 10%, p<0.001).

In seven patients (7.6%) an abnormal stress response was observed; six patients could not increase EF and three patients were not able to decrease ESV during stress. Events developed in four of these seven patients, median 1.3 (0.5 – 4.8) years after the dobutamine CMR.

There were no significant differences at rest nor in stress response between the dominant RV or LV. We also found no relation between RV/LV dominance or AV valve regurgitation and stress response.

Cardiac events

As shown in Table 3, after a median follow-up of 5.8 (4.9 – 10.0) years 23 patients (25%) developed a cardiac event. This event developed at a median of 3.1 (1.5 – 5.7) years after the dobutamine CMR and at a median time of 12.6 (9.7 – 17.8) years after Fontan completion. One patient was listed for heart transplantation.

Table 2. CMR parameters at baseline for patients with and without events

	All patients (n=92)		Patients with events (n=23)		Patients without event (n=69)		P-value event vs no event
	Rest	Stress	Rest	Stress	Rest	Stress	
Median age at baseline (years)	11.5 (9.8-15.3)		13.3 (10.2-16.0)		11.3 (9.7-15.0)		0.193
Mass (g/m²)	61 ± 19		73 ± 23		57 ± 16		<0.001
Mass/EDV ratio (g/ml)	0.75 ± 0.26		0.87 ± 0.35		0.71 ± 0.21		0.048
EDV (ml/m²)	85 ± 21	73 ± 21 *	89 ± 26	76 ± 26 *	84 ± 19	72 ± 19 *	0.369
ESV (ml/m²)	39 ± 16	26 ± 13 *	43 ± 21	32 ± 19 *	38 ± 14	25 ± 11 *, †	0.167
SV (ml/m²)	46 ± 12	47 ± 12	47 ± 14	45 ± 14	46 ± 12	47 ± 12	0.898
EF (%)	55 ± 10	65 ± 10 *	54 ± 12	60 ± 13 *	56 ± 9	67 ± 9 *, †	0.586
Δ stress -rest							
EDV (ml/m²)		- 13 ± 9		- 12 ± 6		- 13 ± 9	0.849
ESV (ml/m²)		- 13 ± 7		- 11 ± 8		- 13 ± 7	0.312
SV (ml/m²)		1 ± 6		- 2 ± 6		1 ± 6	0.051
EF (%)		10 ± 7		6 ± 7		11 ± 6	0.002

Results are given as mean (SD) or as median (25-75th percentile).
* indicates a statistical significant difference between rest vs stress within the subgroup.
† indicates a statistical significant difference between stress within the event vs no event group.
Abbreviations; EDV: end diastolic volume, ESV: end systolic volume, SV: stroke volume EF: ejection fraction.

There was no difference in median age at baseline between the event-group and the non-event group. Moderate to severe AV-valve regurgitation was present in seven (30.4%) of the event-group vs 20 (29.0%) of the non-event group, p=0.895. There was also no significant difference in peak VO_2 (34.4 (24.8 – 39.4) vs 34.1 (28.1 – 39.2 ml/min/kg, p=0.66, n=72), predicted VO_2 peak (77.5 (57.7 – 88.3) vs 84.1 (66.7 – 95.0) %, p=0.14, n=72) or NT-proBNP (13.7 (8.2 – 47.8) vs 10.7 (6.1-22.1) pmol/l), p=0.18, n=83) at baseline for the event vs the non-event group.

Table 2 shows that the event-group has a higher indexed ventricular mass compared to the non-event group. Also the mass volume ratio was statistically higher in the event group vs the non-event group.

Patients who did develop an event had a significantly lower FR during stress compared to the non-event-group (6 ± 7 vs 11 ± 6%, p=0.002). in Figure 1 the event-free survival for the different quartiles of FR is shown. The event-free survival was better for the patients in the highest quartile of FR (Log-rank: 0.024), patients in the highest quartile had a FR ≥14%.

Table 3. Clinical state at latest follow-up

	Patients (n=92)
Median age at latest follow-up (years)	18.6 (16.1-22.1)
Median follow op time since dobutamine CMR (years)	5.8 (4.9-10.0)
Overall cardiac event (n, %)	23 (25.0)
Median time after dobutamine CMR (years)	3.1 (1.5-5.7)
Median time after Fontan completion (years)	12.6 (9.7-17.8)
Cardiac reoperation (n, %)	7 (7.6)
Aortic valve replacement (n, %)	2 (2.2)
AV valve repair and ECC replacement (n, %)	2 (2.2)
ECC replacement (n, %)	1 (1.1)
Conversion to bidirectional Glenn (n, %)	1 (1.1)
Tunnel repair (n, %)	1 (1.1)
Pacemaker (n, %)	5 (5.4)
Ablation/cardioversion of arrhythmias (n, %)	4 (4.3)
Hospitalization for arrhythmias (n, %)	3 (3.3)
Coiling of collaterals (n, %)	1 (1.1)
Stenting of the ECC (n, %)	1 (1.1)
Plastic bronchitis (n, %)	0 (0)
OHCA (n, %)	1 (1.1)
Cardiac death (n, %)	1 (1.1)

Results are given as median (25-75th percentile) or as counts (percentages).
Abbreviations; AV: atrio ventricular, CMR: cardiac magnetic resonance imaging, ECC: extracardiac conduit, OHCA: out-of-hospital cardiac arrest.

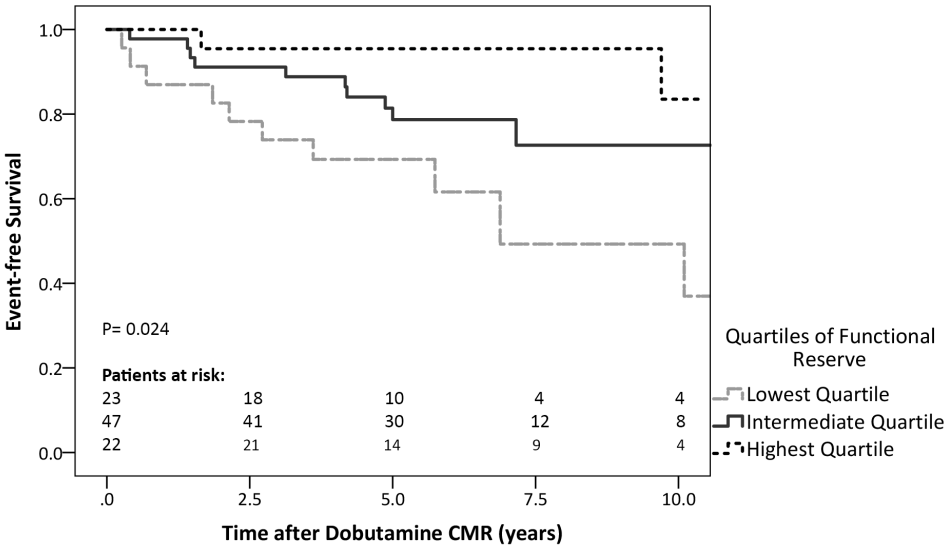
Predictors for events

Univariable analysis showed that FR (HR: 0.88; 95% CI 0.82 –0.95, p=0.001) and cardiac mass (HR: 1.03; 95% CI 1.01 – 1.06, p=0.003) were significantly associated with the risk of an event. FR has a C-index of 0.70 and cardiac mass a C-index of 0.62. NT-proBNP was found borderline predictive for future cardiac events in univariable analysis (HR: 1.02; 95% CI 1.00 – 1.04, p=0.052). Other baseline characteristics were not significantly associated with the risk of cardiac events, see Table 4.

In multivariable analyses with the following two parameters indexed ventricular mass and FR, both FR (HR 0.86; 95% CI 0.79 – 0.93; p<0.001) and indexed ventricular mass (HR 1.04; 95% CI 1.02 – 1.07; p=0.001) were predictive for future cardiac events. Both predictors combined have a C-index of 0.73. However there was no correlation (r=-0.069, p=0.510) between ventricular mass and FR.

If patients with an APC (n=5) are excluded from the analysis, the same parameters remain predictive in multivariable analysis (FR (HR 0.87; 95% CI 0.80 – 0.94; p=0.001) and indexed ventricular mass (HR 1.03; 95% CI 1.00 – 1.07; p=0.030)).

Figure 1. Kaplan-Meier curve for event-free survival for functional reserve



Abbreviations; CMR: cardiac magnetic resonance imaging

Discussion

In this study we have demonstrated that there is a clear relation between ventricular response to low-dose dobutamine stress and subsequent outcome at medium term follow-up, even in a relatively young Fontan population. Patients with a FR of ≥14% (highest quartile) at baseline had significantly fewer events during follow-up. Patients in the lowest quartile, with a FR ≤ 5%, had the highest risk of developing an event during follow-up. Furthermore, ventricular mass did differ statistically between the event vs the non-event group (73 ± 23 vs 57 ± 16 g/m^2, p<0.001).

Patients who have had a Fontan operation are among congenital heart disease patients with the highest risk for late death, circulatory failure, arrhythmias, thromboembolic events, PLE and re-interventions.[7, 24, 25] Parameters that can be used to predict these outcomes are required. In studies that have assessed these parameters composite end-points have been used that include the well-known outcomes, including arrhythmias.[24, 26] Ventricular dysfunction is an independent predictor of ventricular arrhythmias and chronic volume overload related to ventricular dysfunction has been linked to atrial flutter/fibrillation.[26] In previous studies, risk factors derived from CMR have been identified. Death and (being listed for) heart transplantation were associated with higher EDVi (>125 ml/m^2) as assessed with CMR in adolescents with a Fontan circulation.[5, 27] In our present study, only one patient died, at five years after the baseline CMR; this patient had an EDVi of 147 ml/m^2 at baseline. Our findings on ventricular

Table 4. Cox-regression analyses for combined event

	Univariable			Multivariable		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Age at dobutamine CMR (years)	1.07	0.16–1.18	0.16			
Male	1.58	0.62–4.02	0.34			
Age at Fontan (years)	1.05	0.81–1.37	0.70			
Dominant LV	0.91	0.40–2.11	0.40			
Moderate to severe AV-valve regurgitation at baseline	1.41	0.56–3.52	0.47			
NT-proBNP (pmol/l)	1.02	1.00–-1.04	0.052			
Peak VO_2 (% of predicted)	0.98	0.96–1.011	0.23			
Mass (g/m^2)	1.03	1.01–1.01	0.003	1.04	1.02–1.07	0.001
Mass/EDV ratio (g/ml)	3.71	0.86–15.89	0.078			
Rest EDV (ml/m^2)	1.01	0.99–1.03	0.20			
Rest ESV (ml/m^2)	1.02	0.99–1.04	0.057			
Rest SV (ml/m^2)	1.00	0.97–1.04	0.89			
Rest EF (%)	0.98	0.94–1.02	0.33			
FR (%)	0.88	0.82–0.95	0.001	0.86	0.79–0.93	<0.001

Abbreviations; CI: confidence interval, EDV: end diastolic volume, EF: ejection fraction, ESV: end systolic volume, FR: functional reserve, HR: hazard ratio, LV: left ventricle, peak VO_2 : maximum oxygen uptake, SV: stroke volume.

mass confirm earlier observations that in Fontan patients transplantation-free survival is better with lower indexed ventricular mass compared to the Fontan patients who died or received a heart transplantation.[5]

Of the non-imaging derived parameters related to the outcome measures in the Fontan population, such as death, thromboembolic events, arrhythmias, PLE and unplanned cardiovascular hospitalization, peak VO_2 and elevated BNP have been found a predictors for poor outcome.[6, 9, 28-30] In our study we found no significant difference in peak VO_2, percent of predicted VO_2 or in NT-proBNP levels between the event and non-event group. For CPET this may be related to the relatively young age at study of our subjects, since exercise performance is relatively well preserved in young Fontan patients.[21]

Since none of the other previously identified predictors related to outcome in our relatively young patients, who could be considered at relatively low risk, we think stress CMR parameters, particularly FR, may be a useful early marker for outcome in Fontan patients.

Dobutamine is a synthetic catecholamine with a positive inotropic effect.[31] It increases myocardial demand for oxygen in a comparable manner as physical exercise. In healthy volunteers the normal response to stress consist of a decrease in ESVi and a subsequent

increase of EF, while EDVi does not change.[20, 32] We have reported the good clinical tolerance of low dose dobutamine for stress imaging in children with heart disease.[33] In previous studies using dobutamine CMR we have demonstrated that the ventricular response to stress in the Fontan circulation is abnormal: patients were able to increase EF and decrease ESVi, but an abnormal decrease in EDVi was observed.[16, 17] This resulted in no significant increase in SV during stress. More recently, invasive studies in Fontan patients have confirmed this highly abnormal stress response of the univentricular heart after the Fontan operation, using both dobutamine as well as physical stress.[14-16]

Several abnormalities could contribute to the impaired stress response. The geometry of the Fontan baffle and the directly connected vessels (caval veins and pulmonary arteries) has been identified as a source of increased energy loss with increase of cardiac output.[34, 35] Recently, this has been associated with impaired exercise performance.[36]

Another factor is pulmonary vascular resistance (PVR). Invasive studies have shown conflicting results with regard to this factor with increased cardiac output. A decrease of PVR has been demonstrated in young adults with 10 μg/kg/min of dobutamine and with physical stress.[14] In children 8.6 ± 2.3 years of age with HLHS after the Fontan operation no difference in PVR with 10 and 20 μg/kg/min of dobutamine was shown.[15] These observations suggest that a lack of decrease of PVR with increase in cardiac output may be considered abnormal in young Fontan patients and may be related to abnormal pulmonary vascular function in the Fontan circulation.[18, 37] As such, this may impair preload and contribute to an abnormal stress response of the single ventricle. Our results are compatible with impaired ventricular preload during dobutamine stress.[38-41] However, diastolic dysfunction may also be involved. In an earlier study we demonstrated that the ventricular stress response of patients with most signs of diastolic dysfunction of the single ventricle was more abnormal than that of patients with normal diastolic function.[17] Invasive measurements of end-diastolic pressure and of active relaxation have indicated that in HLHS patients after the Fontan operation, diastolic function is normal and that serial changes are limited.[15] Others have shown unfavorable changes in the end-diastolic pressure volume relationship, compatible with abnormal compliance of the single ventricle.[14] Of note, it has been shown that the effect of diastolic dysfunction on ventricular filling during dobutamine stress-testing is negligible.[10, 40, 41] Furthermore, low-dose dobutamine is considered to improve diastolic relaxation.[42] This means that preload impairment, rather than diastolic dysfunction, is more likely the important factor to explain the abnormal stress response.[40, 41]

Other factors to be considered as predictors of adverse outcome are systolic function of the single ventricle and ventriculo-arterial (VA) coupling. Systolic function is generally well preserved in children and adolescent Fontan patients who have had a staged total cavopulmonary approach.[17, 43] Invasive studies have confirmed normal contractility in the large majority of these patients.[14, 15] Abnormal afterload is common in the Fontan circulation. Wong *et al*.[15] recently showed that energetic efficiency as assessed by

measures of VA coupling is well preserved in the single right ventricle in young Fontan patients. In an older and larger group of patients, Saiki *et al*.[44] demonstrated impaired VA coupling and reduced ventricular efficiency, resulting in heightened sensitivity to heart rate of cardiac output. These are factors to consider in the interpretation of functional reserve.

The predictive and diagnostic role of dobutamine stress imaging for the outcome of adult patients with ischemic heart disease has been well established.[13] The relation between stress CMR parameters and hard outcome measures in adult congenital heart disease has only been reported by Winter *et al.*[12] In this study, patients with a systemic RV with an abnormal response to stress had a higher risk of developing cardiac events during 8 years of follow-up. This abnormal stress response, consisting of an inability to increase RVEF or to decrease RVESV, was observed in 17 of the 39 patients in their study. In our study a similar response was noted in seven patients. The differences in percentage abnormal response most likely relates to differences in age and type of disease of the respective patient groups. Both studies indicate that in patients with known impairment of preload during situations with increased demand for cardiac output, dobutamine stress imaging may be helpful in predicting future events. In Fontan patients no other prospective studies with stress CMR are available.

Limitations

We studied a relatively small number of Fontan patients. However compared to existing literature this amount of Fontan patients receiving dobutamine CMR is large. We had not enough statistical power to specify which events were most related to the dobutamine stress response.

Because our CMR scanner has not been suitable for supine leg exercise, the effects of exercise on cardiac function had to be simulated with pharmacologic stress. Because of time constraints in an already relatively long scanning protocol we were not able to perform late gadolinium enhancement in our patients to detect myocardial fibrosis.

Conclusion

Ventricular response to dobutamine stress is a predictor for outcome related events in young patients with a Fontan circulation. Patients with a FR of ≥14% had significantly less events during follow-up.

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Chapter 5

Associations between blood biomarkers, cardiac function and adverse outcome in a young Fontan cohort

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Abstract

Background

Fontan patients are at high risk of circulatory failure. In an exploratory analysis we aimed to determine the prognostic value of blood biomarkers in a young Fontan cohort.

Methods and Results

In multicentre prospective studies Fontan patients underwent blood sampling, cardiopulmonary exercise testing and stress cardiac magnetic resonance imaging (CMR). Several biomarkers including NT-proBNP, GDF-15, Galectin-3, ST-2, DLK-1, FABP4, IGFBP-1, IGFBP-7, MMP-2, and vWF were assessed in blood at 9.6 (7.1-12.1) years after Fontan completion. After this baseline study measurement, follow-up information was collected on the incidence of adverse cardiac events, including cardiac death, out of hospital cardiac arrest, heart transplantation (listing), cardiac reintervention (severe events), hospitalization, and cardioversion/ablation for arrhythmias) was collected and the relation with blood biomarkers was assessed by Cox proportional hazard analyses. The correlation between biomarkers and other clinical parameters was evaluated. We included 133 Fontan patients, median age 13.2 (25^{th},75^{th} percentile 10.4, 15.9) years, median age at Fontan 3.2 (2.5, 3.9) years. After a median follow-up of 6.2 (4.9, 6.9) years, 36 (27.1%) patients experienced an event of whom 13 (9.8%) had a severe event. NT-proBNP was associated with (all) events during follow-up and remained predictive after correction for age, sex and dominant ventricle (HR: 1.89; CI 1.32-2.68). The severe event-free survival was better in patients with low levels of GDF-15 (p=0.005) and vWF (p=0.008) and high levels of DLK-1 (p=0.041). There was a positive correlation (β=0.33, p=0.003) between DLK-1 and stress CMR functional reserve.

Conclusions

NT-proBNP, GDF-15, vWF, DLK-1, ST-2 FABP4 and IGFBP-7 levels relate to long-term outcome in young Fontan patients.

Introduction

Since the introduction of the contemporary modifications of the Fontan operation, which is the treatment of choice in most patients with a functional univentricular heart, long-term survival has improved, resulting in a rapidly increasing number of surviving Fontan patients.[1-4]

However, long-term complications are common and include circulatory failure, thromboembolic events, arrhythmias and death.[1, 4, 5] In general the incidence of heart failure in congenital heart disease (ConHD) patients is 1.2 per 1000 patients-years and increases with age.[6] One- year mortality after admission for heart failure in ConHD patients is 24%.[6] In Fontan patients after atriopulmonary Fontan (which was the original surgical procedure), 28-year freedom from death, heart transplantation or heart failure is only 45%.[2, 7] In children and adolescents who have undergone contemporary modifications of the Fontan operation in a staged approach, the incidence of heart failure seems lower although exact data are lacking.[3, 8] In Fontan patients early identification and treatment of heart failure is important.[2]

Blood biomarkers are a new potential tool in risk stratification in ConHD patients. In recent years various pathways of myocardial stress, inflammation, fibrosis, remodeling and vascularization and related blood biomarkers have been discovered, mostly in adult heart failure patients.[9-13] In previous studies biomarkers such as n-terminal pro-brain natriuretic peptide (NT-proBNP), Galectin-3 (Gal-3), suppression of tumorigenicity 2 (ST2), growth differentiation factor 15 (GDF-15), von Willebrand Factor (vWF) and matrix metalloproteinase 2 (MMP-2) have been related to clinical condition, heart failure or impaired cardiac function in groups of ConHD patients with mixed diagnoses.[9, 12, 14-17] However, in young Fontan patients relatively few biomarkers have been studied. Therefore, the aim of this study was to explore the relationship between levels of multiple promising biomarkers (assessed from the literature) and clinical outcomes in a young contemporary Fontan cohort.

Methods

Because of the sensitive nature of the data collected for this study, the requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

Patients and methods

We included all Fontan patients ≥8 years old with a staged total cavopulmonary connection (TCPC) from whom blood samples taken at a single moment in time were stored in the setting of two cross-sectional and prospective studies in five tertiary referral centers between 2009 and 2018.[18, 19] The institutional review boards of participating centers approved the studies. Patients with contra-indications for cardiac

magnetic resonance imaging (CMR) were excluded. All participants, and if necessary their parents, gave written informed consent before inclusion in these studies. At the baseline study assessment all patients underwent blood sampling, CMR and cardiopulmonary exercise testing (CPET) according to a standard protocol in all contributing centers. The patients were subsequently followed in the setting of usual care, commonly one to two visits / year.

Blood sample analysis

Blood samples were taken from a peripheral vein and collected in EDTA tubes. Samples were stored at −80°C. The frozen samples were shipped to Olink Proteomics AB (Uppsala, Sweden) for analysis with the Olink Cardiovascular panel III. Using proximity extension assay (PEA) technology the levels of biomarkers were measured, this PEA technique has been described extensively before.[20] All blood samples were coded, therefore laboratory staff was blinded for the patients clinical and study data. Likewise the physician did not know the outcomes of the biomarkers assessment. Biomarker levels were not used for clinical decision-making. The biomarker values are presented as normalized protein expression (NPX) units on a Log2 scale.

For the aim of the current study, we examined ten biomarkers that have been associated with ConHD, the Fontan circulation, cardiac fibrosis or heart failure in general.[11, 16, 17, 21-24] These biomarkers were: GDF-15, Gal-3, protein delta homolog 1 (DLK-1), fatty acid-binding protein 4 (FABP4), insulin-like growth factor-binding protein 1 (IGFBP-1), IGFBP-7, NT-proBNP, MMP-2, ST2 and vWF. These biomarkers were selected from the literature prior to the data analysis.

Clinical data

CMR acquisition and analysis

CMR imaging was performed with a dedicated phased-array cardiac surface coil. All images were acquired without sedation during free breathing. Scans were performed at rest and repeated during continuous low-dose (7.5 μg/kg/min) dobutamine-hydrochloride infusion (Centrafarm Services, Etten-Leur, the Netherlands). Dobutamine infusion was decreased to 5.0 μg/kg/min (or if necessary stopped) when the heartrate increased >50%, when the systolic and/or diastolic blood pressure increased >50% or decreased <20%, when rhythm disturbances were seen, or with complaints of the patient. Details on our dobutamine stress protocol have been published previously.[18, 25]

Analyses were performed with the software packages MASS and FLOW (Medis Medical Imaging Systems, Leiden, the Netherlands). Contours were manually drawn in end-diastole and end-systole, papillary muscle and trabeculae were excluded from the blood pool. All CMR's were analysed by one of the authors (EvdB) under supervision of one of the authors (WH) with longstanding experience in CMR. End diastolic volume (EDV) and end-systolic volume (ESV) were obtained and used to calculate ejection fraction (EF). Ventricular volumes were defined as the sum of the volumes of the

systemic ventricle and the hypoplastic chamber. All ventricular volumes were indexed for body surface area. Data on the reproducibility of the CMR analyses have previously been published by our group.[26]

Changes in CMR parameters during dobutamine stress were calculated as follows: parameter change (Δ) = $parameter_{stress}$ – $parameter_{rest}$, functional reserve (FR) is described as the EF_{stress} – EF_{rest}.[5]

Cardiopulmonary exercise tests

CPETs were performed on a bicycle ergometer according to protocols used in previous studies by our group.[18, 25] From these exercise tests the peak oxygen uptake (VO_2) was assessed and expressed as percentage of predicted values. Exercise tests with a peak respiratory exchange rate of ≥1.0 were included in the analysis.

Study endpoint

After the baseline study assessment, patients received regular patient specific care. For the purpose of the current study the medical records of the latest outpatients visit were reviewed and all cardiac events during follow-up (since the baseline study measurement) were recorded until June 2018. The survival status of the patients was also checked in the Municipal Population Register.

Severe events were defined a death, out of hospital cardiac arrest (OHCA), heart transplantation (listing) or cardiac reoperations. Overall events included the severe events as well as cardiac reintervention and hospitalization or cardioversion/ablation for arrhythmias.

Patients who experienced multiple events were considered to have reached the study endpoint at the time of the first event.

Statistical methods

Continuous baseline variables are summarized as mean value ± standard deviation (SD), and as median value (25^{th}, 75^{th} percentile). Differences between patients with and without events were analysed using Mann-Whitney U tests. Categorical variables are presented as numbers and percentages, whereas between-group differences are evaluated by chi-squared tests, or Fischer's exact tests (in case expected values <5).

Linear regression analysis is applied to study the relation between the selected biomarkers with CPET, CMR and clinical parameters, while adjusting for age and sex.

We applied Cox proportional hazard regression analyses to explore the association between the selected biomarkers and the incidence of the specified study endpoints. Biomarkers were entered as standardized continuous variables (Z-score). We report hazard ratios (HR) with corresponding 95% confidence interval (CI), which are estimated using Firth's method for bias reduction in small samples. For 'overall' events we present regression results as a) unadjusted HRs, b) HRs that are adjusted for age and sex, and c) HRs that are adjusted for age, sex and dominant ventricle. For 'severe' events we only present unadjusted HRs, since the number of such events was limited.

The Cox regression model provides a relative measure of association between the explanatory variable (i.e. the biomarker) and the study endpoint. We produced Kaplan-Meier event-free survival curves in order to also provide an impression of the relation between biomarker levels and absolute incidences. For that particular purpose, patients were categorized by quartiles (quartile 1-2 vs quartile 3-4) of the corresponding biomarker, whereas differences between groups were evaluated using the log-rank test, in particular the permutation version (in view of the relative small number of events).

Analyses were performed using SPSS (version 24.0) and R (version 4.0.0; mainly the 'coin' and 'coxphf' packages) statistical software. Two-sided p-values <0.05 are considered statistically significant.

Results

A total of 133 patients were included in this analysis at a median of 9.7 (7.1, 12.1) years after the Fontan operation. The median age at the baseline study assessment was 13.2 years (10.4, 15.9). At baseline a CMR was performed in 119 patients and a successful CPET was performed in 103 patients. The available blood sample was successfully analysed in all 133 patients. Table 1 shows patient characteristics in relation to study endpoint events.

Overall events and baseline characteristics

During a median follow-up of 6.2 (4.9, 6.9) years since the baseline study assessment, 36 (27.1%) patients experienced an overall event (see Table 2). The main cause for overall events were cardiac catheter interventions. One patient experienced an out of hospital cardiac arrest and received an implantable cardioverter-defibrillator.

There was no difference in median age or other surgical or baseline characteristics between the patients who did and did not develop an event during follow-up. Patients with an event had a significantly diminished increase in EF during dobutamine stress CMR (functional reserve (FR)), 5 ± 6 vs 10 ± 6 %, p=0.001.[5]

Overall events and biomarkers

Results of Cox regression analyses relating the selected biomarkers 'overall events' are given in Table 3. It appeared that only NT-proBNP was significantly associated with the incidence of an 'overall event'. After adjustment for age, sex and dominant RV, the HR for a 1-SD difference was 1.88 (95% CI 1.31 - 2.69, p=0.001). ST2 was also associated with 'overall events', but statistical significance was not reached (adjusted HR for 1 SD difference 1.38; 95% CI 0.98-1.89; p=0.063).

Table 1. Baseline patient characteristics in patients who reached study endpoints and those who remained event-free

	Overall event	No overall event	p-value	Severe event*	No severe event	p-value
No. of patients	*36*	*97*		*13*	*120*	
Age at baseline (years)	13.9 ± 4.9	13.9 ± 4.2	0.98	15.8 ± 5.4	13.7 ± 4.3	0.097
	12.9 (9.8, 15.5)	13.2 (10.4, 16.2)	0.67	14.8 (11.2, 20.9)	12.9 (10.4, 15.8)	0.16
Male (n, %)	20 (55.6)	55 (56.7)	1	10 (76.9)	65 (54.2)	0.15
Resting saturation (%)	94 ± 5	95 ± 3	0.23	95 ± 3	95 ± 3	0.94
	95 (93, 97)	95 (94, 97)	0.58	95 (94, 98)	95 (94, 97)	0.98
Length (cm)	152 ± 17	157 ± 15	0.17	160 ± 18	155 ± 16	0.30
	151 (137, 166)	156 (144, 168)	0.16	160 (144, 177)	155 (142, 167)	0.37
Weight (kg)	44 ± 17	47 ± 15	0.32	51 ± 19	46 ± 15	0.23
	38 (30, 54)	46 (34, 58)	0.19	48 (36, 63)	43 (33, 57)	0.35
BSA (m^2)	1.35 ± 0.33	1.42 ± 0.29	0.25	1.50 ± 0.35	1.39 ± 0.30	0.25
	1.26 (1.09, 1.57)	1.44 (1.09, 1.64)	0.16	1.47(1.20, 1.75)	1.38 (1.13, 1.63)	0.38
Dominant ventricle						
Left (n, %)	24 (66.7)	60 (61.9)	0.69	9 (69.2)	75 (62.5)	0.77
Right (n, %)	11 (30.6)	36 (37.1)	0.54	4 (30.8)	43 (35.8)	1.00
Indifferent (n, %)	1 (2.8)	1 (1.0)	0.47	0 (0.0)	2 (1.7)	1.00
Cardiac diagnosis						
HLHS (n, %)	8 (22.2)	12 (12.4)	0.18	3 (23.1)	17 (14.2)	0.41
Tricuspid atresia (n, %)	11 (30.6)	30 (30.9)	1.00	5 (38.5)	36 (30.0)	0.54
Pulmonary atresia (n, %)	4 (11.1)	11 (11.3)	1.00	1 (7.7)	14 (11.7)	1.00
DILV (n, %)	6 (16.7)	13 (13.4)	0.59	2 (15.4)	17 (14.2)	1.00
DORV (n, %)	3 (8.3)	18 (18.6)	0.19	1 (7.7)	20 (16.7)	0.69
Other (n, %)	4 (11.1)	13 (13.4)	1.00	1 (7.7)	16 (13.3)	1.00

Table 1. Continued

	Overall event	No overall event	p-value	Severe event*	No severe event	p-value
Age at Fontan procedure (years)	3.2 ± 1.1	3.5 ± 1.3	0.31	3.5 ± 1.5	3.4 ± 1.3	0.88
	3.2 (2.4, 3.9)	3.2 (2.6, 3.9)	0.54	3.3 (2.4, 4.3)	3.2 (2.5, 3.9)	0.90
Type of Fontan						
ECC (n, %)	20 (60.6)	56 (58.9)	0.85	6 (46.2)	70 (58.3)	0.56
ILT (n, %)	13 (39.4)	39 (41.1)	0.70	6 (46.2)	46 (38.3)	0.77
Other (n, %)	3 (8.3)	2 (2.1)	0.12	1 (7.7)	4 (3.3)	0.41
Maximal exercise parameters	*n= 24*	*n= 79*		*n= 11*	*n= 92*	
Peak VO_2 (ml/min/kg)	32.1 ± 8.5	33.1 ± 6.8	0.55	33.3 ± 9.7	32.8 ± 6.9	0.85
	33.5 (24.4, 38.8)	32.4 (28.2, 38.0)	0.59	36.1 (23.6, 40.4)	32.2 (28.0, 38.0)	0.81
Peak VO_2 (% of predicted)	78.3 ± 18.1	82.1 ± 15.9	0.32	77.9 ± 22.1	81.6 ± 15.7	0.48
	77.3 (64.4, 92.7)	81.5 (69.5, 92.6)	0.34	78.2 (55.0, 93.8)	80.7 (69.7, 92.6)	0.66
CMR	*n= 32*	*n= 87*		*n= 11*	*n= 108*	
EDV (ml/m^2)	97 ± 34	90 ± 19	0.28	118 ± 43	89 ± 20	0.053
	85 (72, 102)	87 (76, 101)	0.75	99 (94, 140)	86 (76, 100)	0.006
ESV (ml/m^2)	47 ± 29	42 ± 12	0.28	65 ± 41	41 ± 12	0.078
	40 (31, 52)	40 (33, 48)	0.71	57 (49, 62)	39 (32, 48)	0.002
SV (ml/m^2)	48 ± 14	48 ± 11	0.67	53 ± 13	48 ± 12	0.25
	47 (41, 54)	46 (42, 58)	0.97	47 (45, 65)	46 (51, 54)	0.27
EF (%)	53 ± 10	54 ± 7	0.54	47 ± 11	54 ± 8	0.007
	53 (46, 60)	54 (50, 59)	0.64	47 (44, 56)	55 (49, 60)	0.023
Mass (g/m^2)	61 ± 19	56 ± 15	0.10	67 ± 19	56 ± 16	0.037
	57 (46, 71)	53 (44, 65)	0.22	71 (52, 76)	53 (45, 65)	0.036
Mass/EDV ratio (g/ml)	0.66 ± 0.24	0.63 ± 0.15	0.32	0.58 ± 0.10	0.64 ± 0.18	0.24
	0.62 (0.53, 0.74)	0.61 (0.51, 0.74)	0.73	0.61 (0.48, 0.64)	0.62 (0.52, 0.75)	0.23

Δ Stress: Stress - Rest CMR	*n= 19*	*n= 57*		*n= 8*	*n= 68*	
EDV (ml/m^2)	-15 ± 13	-12 ± 9	0.31	-12 ± 11	-13 ± 10	0.75
	-12 (-21, -6)	-10 (-18, -5)	0.51	-11 (-24, 0)	-10 (-18, -5)	0.79
ESV (ml/m^2)	-10 ± 9	-13 ± 7	0.13	-10 ± 9	-13 ± 7	0.37
	-9 (-14, -4)	-13 (-17, -9)	0.057	-6 (-21, -3)	-12 (-17, -9)	0.36
SV (ml/m^2)	-4 ± 8	2 ± 7	0.005	-1 ± 5	0 ± 8	0.61
	-3 (-6, 0)	2 (-2, 6)	0.005	-3 (-4, 3)	0 (-3, 6)	0.28
EF (%)	5 ± 6	10 ± 6	0.001	5 ± 4	10 ± 7	0.033
	5 (1, 9)	10 (6, 15)	0.002	5 (1, 7)	10 (5, 14)	0.016

*Definition severe event: death, OHCA, heart transplantation (listing) or cardiac reoperations

Continuous baseline variables are summarized as mean value ± standard deviation (SD), and as median value (25th-75th percentile). Categorical variables are presented as numbers and percentages.

Abbreviations; BSA: body surface area, HLHS: hypoplastic left heart syndrome, DILV: Double inlet left ventricle, DORV: Double outlet right ventricle, ILT: intra-atrial lateral tunnel, ECC: extra cardiac conduit, VO_2 peak: maximum oxygen uptake, CMR: cardiovascular magnetic resonance imaging, EDV: end diastolic volume, ESV: end systolic volume, SV: stroke volume, EF: ejection fraction.

Table 2. Clinical state at latest follow-up

	Patients (n=133)
Median age at latest follow-up (years)	18.3 (16.0, 21.8)
Median time after blood sampling (years)	6.2 (4.9, 6.9)
First overall event (n, %)	36 (27.1)
Median time after study until first overall event(years)	2.8 (1.1, 4.7)
Median time after Fontan until first overall event (years)	12.6 (9.7, 17.1)
OHCA, survived (n, %)	1 (0.8)
Cardiac reoperation (n, %)	8 (6.0)
Cardiac catheter intervention (n, %)	13 (9.8)
Hospitalization/ablation for arrhythmias (n, %)	12 (9.0)
Implantation pacemaker (n, %)	2 (1.5)
Second overall event (n, %)	12 (9.0)
Severe event* (n, %)	13 (9.8)
Deceased (n, %)	1 (0.8)
OHCA, survived (n, %)	1 (0.8)
Heart transplantation listing (n, %)	1 (0.8)
Cardiac reoperation (n, %)	10 (7.5)
ECC replacement (n, %)	3 (2.3)
Closure tunnel leakage (n, %)	2 (1.5)
Bentall procedure (n, %)	2 (1.5)
Mitral valve replacement (n, %)	1 (0.8)
Other (n, %)	2 (1.5)

Continuous variables are summarized as mean value ± standard deviation (SD), and as median value (25^{th}-75^{th} percentile). Categorical variables are presented as numbers and percentages.

*Definition severe event: death, OHCA, heart transplantation (listing) or cardiac reoperations

Abbreviations; OHCA: out of hospital cardiac arrest, ECC: Extra cardiac conduit

Severe events and biomarkers

A total of 13 (9.8%) patients experienced a severe event during follow-up, see Table 1. There were no statistically significant differences in median age or other surgical or baseline characteristics between the patients with and without a severe event. Patients with a severe event had a lower baseline EF, a higher ventricular mass and a lower FR compared to patients without a severe event.[5]

The severe event-free survival was better in patients with lower levels of vWF (p=0.008). In addition patients with the highest DLK-1 levels (p= 0.041) end lowest GDF-15 levels (p=0.005) experienced the best severe event-free survival (see Figure 1). In a univariable Cox regression model, higher levels of NT-proBNP, ST2 and vWF were associated with severe events during follow-up (Table 4).

Table 3. Cox-regression analyses for biomarkers and the overall events

	Crude univariable model			Model adjusted for age and sex			Clinical model*		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Levels (per 1 SD difference)									
DLK-1	0.85	0.62 - 1.18	0.335	0.86	0.61 - 1.20	0.369	0.86	0.61 - 1.21	0.382
FABP4	1.28	0.92 - 1.77	0.141	1.28	0.91 - 1.77	0.148	1.29	0.93 - 1.78	0.129
Gal-3	1.04	0.77 - 1.33	0.776	1.04	0.77 - 1.33	0.784	1.03	0.77 - 1.32	0.823
GDF-15	1.11	0.83 - 1.46	0.468	1.11	0.80 - 1.50	0.529	1.12	0.81 - 1.52	0.482
IFGBP-1	1.15	0.83 - 1.61	0.400	1.16	0.83 - 1.62	0.390	1.14	0.82 - 1.60	0.428
IFGBP-7	1.27	0.93 - 1.76	0.137	1.29	0.94 - 1.79	0.117	1.32	0.95 - 1.81	0.097
MMP-2	1.19	0.85 - 1.65	0.305	1.21	0.86 - 1.69	0.266	1.23	0.88 - 1.70	0.224
NT-proBNP	1.72	1.25 - 2.33	0.001	1.90	1.33 - 2.70	0.001	1.89	1.32 - 2.68	0.001
ST2	1.35	0.98 - 1.80	0.065	1.38	0.99 - 1.89	0.060	1.38	0.98 - 1.89	0.063
vWF	1.27	0.91 - 1.74	0.153	1.31	0.93 - 1.83	0.116	1.31	0.93 - 1.82	0.118

*Clinical model: cox model adjusted for age, sex and single ventricle type

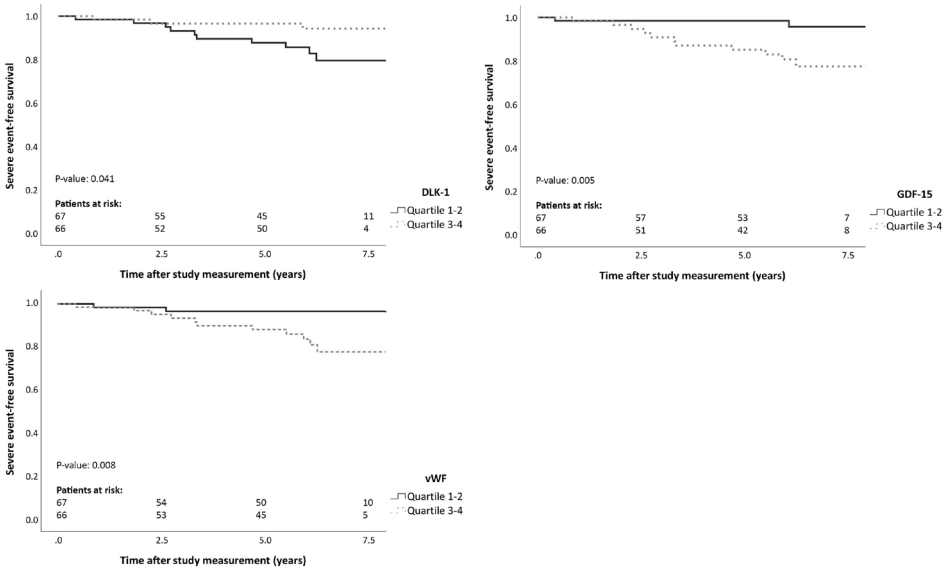
Abbreviations; HR: hazard ratio, CI: confidence interval, DLK-1: protein delta homolog 1, FABP4: Fatty acid-binding protein 4, Gal 3: galectin 3, GDF-15: growth differentiation factor 15, IGFBP-1: insulin-like growth factor-binding protein 1, IGFBP-7: insulin-like growth factor-binding protein 7, MMP-2: matrix metalloproteinase-2 , NT-proBNP: N-terminal pro-brain natriuretic peptide, ST2: suppression of tumorigenicity 2, vWF: von Willebrand factor.

Table 4. Cox-regression analyses for biomarkers and severe events.

	Crude univariable model		
	HR	**95% CI**	**P-value**
Levels (per 1 SD difference)			
DLK-1	0.62	0.37 - 1.06	0.084
FABP4	1.70	0.99 - 2.85	0.053
Gal-3	0.98	0.53 - 1.55	0.952
GDF-15	1.49	0.96 - 2.19	0.073
IFGBP-1	1.40	0.82 - 2.42	0.218
IFGBP-7	1.42	0.82 - 2.50	0.216
MMP-2	1.40	0.81 - 2.35	0.227
NT-proBNP	2.01	1.27 - 3.08	0.004
ST2	1.67	1.02 - 2.54	0.040
vWF	1.77	1.05 - 2.94	0.032

Abbreviations; HR: hazard ratio, CI: confidence interval, DLK-1: protein delta homolog 1, FABP4: Fatty acid-binding protein 4, Gal 3: galectin 3, GDF-15: growth differentiation factor 15, IGFBP-1: insulin-like growth factor-binding protein 1, IGFBP-7: insulin-like growth factor-binding protein 7, MMP-2: matrix metalloproteinase-2 , NT-proBNP: N-terminal pro-brain natriuretic peptide, ST2: suppression of tumorigenicity 2, vWF: von Willebrand factor.

Figure 1. Kaplan-Meier curves for severe event-free survival for the lowest vs highest quartiles of DLK-1, GDF-15 and vWF.



Abbreviations; DLK-1; protein delta homolog 1, GDF-15; growth differentiation factor – 15, vWF: von Willebrand factor.

Association biomarkers with other clinical parameters

In Table 5 associations, corrected for age and sex, between the biomarkers and several baseline CMR and CPET parameters are shown. DLK-1 was associated with FR; for every percent of increase in FR, DLK-1 increased with a factor β=0.33, p=0.003.

Discussion

In this explorative, prospective multicenter study in young Fontan patients we demonstrated an association of several blood biomarkers and ventricular functional reserve (FR) with clinical condition and events during 6 years of follow-up. We observed that NT-proBNP, vWF, DLK-1, ST2 and GDF-15 were related with clinical events during follow-up. Other biomarkers such as FABP-4 and IGFBP-7 seemed associated with parameters of cardiac function. Although the observed relations resemble findings of previous studies (primarily in acquired heart disease) and can be understood from pathological point of view (as we will discuss below), we still consider these as hypothesis generating, given the explorative nature of our study and the broad range of biomarkers studied.

Table 5. Association between study parameters and biomarker levels, corrected for age and sex

Dependent variable		VO_2 max (per 1 ml/min/kg)	EF (Per 1%)	Functional reserve (ΔEF) (Per 1%)
	β	-0.02	0.07	0.33
DLK-1	95% CI	-0.02 – 0.02	-0.01 – 0.02	0.01 – 0.05
	p-value	0.82	0.42	0.003
	β	-0.38	0.17	-0.05
FABP4	95% CI	-0.05 – -0.01	-0.02 – 0.001	-0.02 – 0.02
	p-value	<0.001	0.061	0.65
	β	-0.03	0.12	0.11
Gal-3	95% CI	-0.01 –-0.01	-0.004 – 0.02	-0.01 – 0.02
	p-value	0.77	0.23	0.36
	β	-0.15	-0.15	-0.04
GDF-15	95% CI	-0.03 – 0.004	-0.02 – 0.002	-0.02 – 0.02
	p-value	0.14	0.090	0.75
	β	-0.07	-0.05	0.14
IGFBP-1	95% CI	-0.05 – -0.02	-0.03 – 0.02	-0.02 – 0.06
	p-value	0.51	0.62	0.26
	β	-0.27	-0.245	0.05
IGFBP-7	95% CI	-0.03 – -0.004	-0.02 – -0.00	-0.01 – 0.02
	p-value	0.013	0.009	0.71
	β	-0.20	0.16	0.09
MMP-2	95% CI	-0.02 – 0.001	-0.02 – 0.001	-0.01 – 0.02
	p-value	0.072	0.094	0.46
	β	-0.19	-0.04	-0.20
NT-proBNP	95% CI	-0.07 – 0.003	-0.03 – 0.02	-0.08 – 0.003
	p-value	0.069	0.66	0.069
	β	-0.07	-0.11	0.20
ST2	95% CI	-0.02 – 0.01	-0.02 – 0.005	-0.002 – 0.04
	p-value	0.49	0.23	0.075
	β	-0.04	0.002	0.02
vWF	95% CI	-0.02 – 0.02	-0.02 – 0.02	-0.02 – 0.03
	p-value	0.73	0.98	0.88

Interpretation: for every difference in ml/m^2 or %, the biomarker difference is a factor β.

Abbreviations; NS; not significant, VO_2 max: maximum oxygen uptake, EF: ejection fraction, DLK-1: protein delta homolog 1, FABP4: Fatty acid-binding protein 4, Gal 3: galectin 3, GDF-15: growth differentiation factor 15, IGFBP1: insulin-like growth factor-binding protein 1, IGFBP-7: insulin-like growth factor-binding protein 7, MMP-2: matrix metalloproteinase-2 , NT-proBNP: N-terminal pro-brain natriuretic peptide, ST2: suppression of tumorigenicity 2, vWF: von Willebrand factor.

Fontan patients are at high risk for late death, arrhythmias, and re-interventions.[1, 2, 4] Even in our young (median age 13.2 years) cohort of Fontan patients 27% experienced an event during midterm follow-up, in 9.8% this was a severe event. These observations provide information hardly available so far on the level of events in this age-cohort after Fontan operations with contemporary strategies and point towards the importance of risk-stratification even in relatively young Fontan patients.

Potentially, assessment of blood biomarkers levels is a relatively simple and harmless method to monitor the clinical condition. Since there may be differences in pathways involved in heart/circulatory failure in children with ConHD compared to adults with heart failure, including adults with ConHD, assessment of markers in young patients is important.[12, 13, 27] As such, our study explored biological pathways that are involved in the maintenance of cardiac function and mid- to long-term outcome in a young Fontan cohort.

Fontan failure is generally divided in ventricular failure, systemic venous failure and pulmonary vascular failure.[2] Common pathways that are most likely involved in the development of heart failure in ConHD relate to myocardial hypertrophy, inflammation, fibrosis, remodeling, vascularization, cardiac metabolism and repair.[27] The biomarkers we found which were associated with an increased risk for poor clinical outcome have been associated with ventricular failure and fibrosis (NT-proBNP, GDF-15, DLK-1) or potential endothelial failure (vWF).[11, 28-31] A potentially highly interesting finding in this setting is that of IGFBP-7, since this factor has been associated with cardiac regeneration in zebrafish and mice.[32]

We will subsequently discuss the biological role of these blood biomarkers and associations with clinical outcomes in our study. [11, 16, 17, 21-24]

NT-proBNP

NT-proBNP is secreted mainly by the ventricle as response to increased myocardial stress and ventricular volume and pressure overload.[28] It is a well-known biomarker in acquired heart failure and adult ConHD patients; elevated NT-proBNP levels are associated with mortality and adverse events.[12, 24, 28, 33, 34] In asymptomatic Fontan patients NT-proBNP levels are often within the normal range,[34] but elevated NT-proBNP levels have been associated with an older surgical technique and impaired ventricular function.[24, 35] Although associations between elevated NT-pro(BNP) levels and adverse outcome have been observed,[28, 34, 36] monitoring of (NT-pro)BNP is not specifically mentioned in recent international guidelines for the follow-up of Fontan patients.[37] Our results highlight the potential value of NT-proBNP in the routine follow-up of young Fontan patients.

vWF

vWF is produced mainly in de endothelial cells. In recent years it has emerged as a mediator of inflammation.[29, 30] vWF levels have been associated with an increased risk of myocardial infarction, cerebral stroke and coronary artery disease.[29, 38] In ConHD

patients and especially in Fontan patients, the role of elevated vWF and an elevated risk of thrombosis has been evident.[30, 39] Beyond thrombosis and hemostasis vWF has been associated with adverse events in ConHD.[17] We noted that higher vWF levels are associated with a worse severe event-free survival. None of the events in our patients was thromboembolic.

DLK-1

DLK-1 is a member of the epidermal growth factor-like family.[11] DLK-1 plays a role in angiogenesis, muscular differentiation and in fibrosis.[11, 40] DLK-1 knock-out mice display increased collagen deposition, LV dilatation and reduced myocardial contractility.[11] In human ischemic myocardial tissue DLK-1 mRNA expression was down-regulated compared to healthy tissue.[11] In our study, Fontan patients with higher DLK-1 levels have a better severe-event-free survival. Also, higher DLK-1 levels were associated with a higher FR during dobutamine stress CMR. We recently showed that higher FR is associated with a better event-free survival in young Fontan patients in whom other known predictors did not differentiate between events.[5]

Our findings, combined with the existing literature, indicate a potential role of DLK-1 in the maintenance of cardiac function.

ST2

ST2 is a member of the interleukin-1 receptor family and can be expressed in a soluble form (sST2) and a transmembrane form (ST2 ligand).[9, 22] ST2 is upregulated in response to myocardial stress and is a marker for inflammation and remodeling, fibrosis and apoptosis in the myocardium.[9, 22, 41] In acquired heart failure, higher ST2 levels have been associated with adverse outcomes.[41] In large cohorts (n=602 and n=169) of adult ConHD patients with mainly biventricular circulations, patients with complex ConHD displayed higher sST2 levels, which predicted all-cause mortality and events during follow-up.[9, 22] Likewise in children with several types of ConHD, elevated pre- and postoperative ST2 levels have been associated with 30-day re-admission rate and mortality.[42] In another pediatric ConHD cohort (n=36), including a range of defects, a negative correlation between sST2 levels and left ventricular EF was observed.[21]

In our cohort, higher ST2 levels at baseline were associated with severe events during follow-up. Indicating a possible role for ST2 in the clinical follow-up of young Fontan patients.

GDF-15

GDF-15 is a member of the transforming growth factor beta (TGFβ) family and during ischemia, oxidative stress or reperfusion it is expressed in the heart.[31] GDF-15 is also involved in several cancers, diabetes and may inhibit body-growth, potentially contributing to the 'failure to thrive' mechanism.[31, 43] In ConHD adults, higher GDF-15 levels correlate with poor functional status, cardiac dysfunction, lower VO_2 max, elevated pulmonary pressure and adverse outcome.[15, 24, 31] A small (n=38) study in young

(15.0 years) Fontan patients observed that patients with an echocardiographic EF <50% had significantly higher GDF-15 levels compared to patients with preserved systolic function.[44] Higher GDF-15 levels were associated with reduced severe event-free survival in our Fontan cohort, not with max VO_2.[31] However max VO_2 values in ConHD children are often more preserved compared to ConHD adults.[4]

IGFBP-7

Insulin-like growth factor-binding proteins (IGFBPs) are a family of proteins that regulate and modulate IGF activity and have indirect effects on growth hormone (GH).[45] IGFBP-7 is highly expressed in endothelial cells and has been linked to collagen deposition.[46-48] Interestingly, IGFBP-7 has been linked to post infarction myocardial repair.[32] In both mouse and zebrafish heart regeneration, infarct border zone cardiomyocytes seem to be the most prone to divide. IGFBP7 is upregulated in this border zone of the injured mouse and zebrafish heart, suggesting a role in cardiac regeneration.[32] IGFBP-7 has been identified as potential biomarker for the prediction of adverse outcome in acquired heart failure patients,[23] and is associated with LV diastolic dysfunction and lower VO_2 max.[47] In ConHD patients, the role of IGFPBs in cardiac function or prognosis is largely unexplored, but has been linked to general growth, failure to thrive and nutritional status.[49, 50] Our study is, to our knowledge, the first study in ConHD and Fontan patients that observed an association between IGFBP-7 levels and cardiac function and VO_2 max.

FABP-4

FABP-4 is highly expressed in adipocytes and elevated levels of FABP-4 are associated with adiposity, female sex, diabetes and systemic hypertension.[23, 51, 52] FABP-4 displays some expression in macrophages. It is thought that in macrophages FABP-4 increases foam cell formation and induces an inflammatory response.[51, 52]

FABP-4 levels have been associated with LV hypertrophy and systolic and diastolic dysfunction.[51] In patients with chronic heart failure, higher FABP-4-levels were independently associated with adverse outcome during follow-up.[23] In ConHD patients little is known about FABP-4. Although in our study higher FABP-4 levels were not associated with events, higher FABP-4 levels were associated with lower peak VO_2. A diminished peak VO_2 is a known predictor for poor outcome in ConHD.[53] FABP-4 may be a potential biomarker in ConHD and therefore further research on the role of FABP-4 levels in ConHD is required to assess its value in clinical practice.

Limitations

We studied a total of 133 Fontan patients, which can be considered a small sample. However, compared to the existing literature on biomarker assessment in Fontan patients our sample is relatively large. The Fontan patients in our study were relatively young and in good clinical condition, therefore the number of hard endpoints during follow-up was limited. This is a known limitation in ConHD research.[37] Due to the limited

number of endpoints, especially severe events, it is possible that we have missed associations between biomarkers and endpoints in this study. For this reason, we also could not assess the additional value of combining different biomarkers to predict end-points. At the other hand, we acknowledge that false positives are a competing explanation for some of the found associations, as we did not adjust for multiple testing. And finally, although we did adjust for age and sex in an additive model, we are aware of the possibility of residual confounding. We consider our explorative study mainly as hypothesis generating.

In our study we assessed some of the biomarkers of the Olink cardiovascular III panel to detect possible patterns between biomarkers and cardiac outcome. We did not assess all the measured biomarkers of the Olink panel. Detecting biomarker cut-off values for clinical use was not part of this study and further research is necessary to determine the possible role of the observed biomarkers in clinical practice.

Late gadolinium enhancement or T1 mapping, useful in detecting local or generalized fibrosis in the myocardium, was not performed in our imaging protocol due to time constraints.[54] Therefore we could not investigate associations between myocardial fibrosis with potential fibrosis blood biomarkers.

Conclusions

In this explorative, prospective multicentre study, we performed an analysis of blood biomarkers and their relation to cardiac function and subsequent outcome in a young and contemporary Fontan population. We observed that in addition to NT-proBNP, ST2 and GDF-15, biomarkers such as DLK-1, vWF, FABP-4 and IGFBP-7 relate to cardiac function and long-term outcome, as did the ventricular response to dobutamine stress CMR.[5] These biomarkers, especially NT-proBNP, may have a role in the clinical follow-up and risk stratification of Fontan patients.

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Part II

Tetralogy of Fallot

Chapter 6

Current outcomes and treatment of Tetralogy of Fallot

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Abstract

Tetralogy of Fallot (ToF) is the most common type of cyanotic congenital heart disease. Since the first surgical repair in 1954, treatment has continuously improved. The treatment strategies currently used in the treatment of ToF result in excellent long-term survival (30 year survival ranges from 68.5% to 90.5%). However, residual problems such as right ventricular outflow tract obstruction, pulmonary regurgitation, (ventricular) arrhythmia are common and often require re-interventions.

Right ventricular dysfunction can be seen following longstanding pulmonary regurgitation and/or stenosis. Performing pulmonary valve replacement or relief of pulmonary stenosis before irreversible right ventricular dysfunction occurs is important, but determining the optimal timing of pulmonary valve replacement is challenging for several reasons.

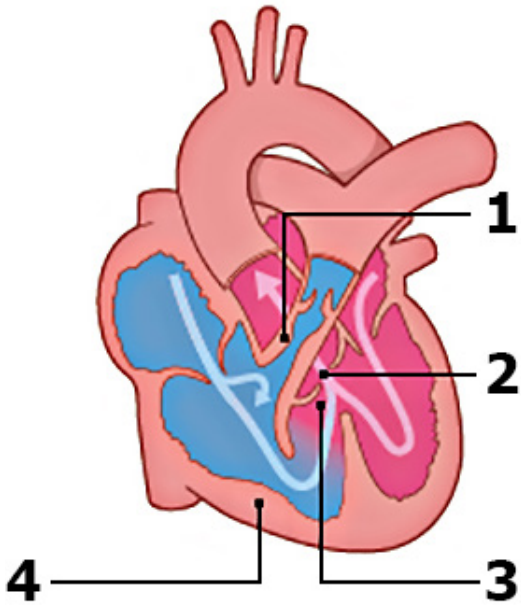
The biological mechanisms underlying dysfunction of the right ventricle as seen in longstanding pulmonary regurgitation are poorly understood. Different methods of assessing the right ventricle are used to predict impending dysfunction. The atrioventricular, ventriculo-arterial and interventricular interactions of the right ventricle play an important role in right ventricle performance, but are not fully elucidated.

In this review we present a brief overview of the history of ToF, describe the treatment strategies currently used, and outline the long-term survival, residual lesions, and re-interventions following repair. We discuss important remaining challenges and present the current state of the art regarding these challenges.

Introduction

Tetralogy of Fallot (ToF), the most common type of cyanotic congenital heart disease (CHD), has an incidence of 0.34 per 1000 live births.[1] The classic tetrad (Figure 1) was first described in 1673 by bishop and anatomist Nicolas Steno, but the anatomy was more extensively described by the French physician Étienne-Louis Fallot in 1888.[2, 3] Patients with ToF have varying degrees of cyanosis depending on the severity of right ventricular outflow tract (RVOT) stenosis and pulmonary artery (PA) anatomy. The anatomic abnormalities seen in ToF vary from milder to more severe phenotypes, such as ToF with pulmonary atresia and Fallot-type double outlet right ventricle (RV). These more severe forms may require different management and treatment strategies. This review focuses on the "classic" ToF, with right ventricular outflow (pulmonary) stenosis, rather than atresia, and excluding double outlet right ventricle.

Figure 1. Schematic overview of the defects seen in Tetralogy of Fallot



Modified from Englert et al.[174] with permission from the publisher.

1) Pulmonary stenosis. **2)** Overriding aorta. **3)** Malalignment ventricular septal defect. **4)** Right ventricular hypertrophy.

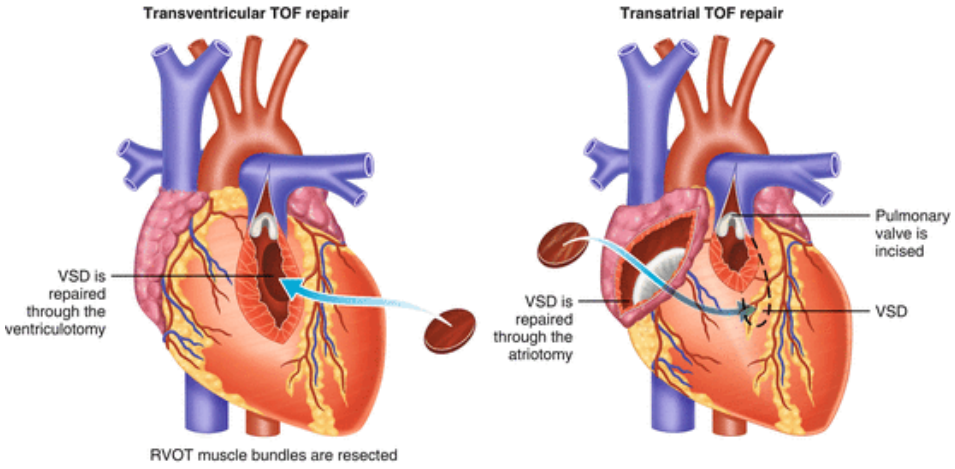
Surgical approaches to repair

Surgical repair of ToF was first described in 1955 by Lillehei *et al*.[4] The right ventricular outflow tract obstruction (RVOTO) was approached by a ventriculotomy into the right

ventricular anterior wall and relief included inserting a transannular patch (TAP) if required (Figure 2, left). Aggressive RVOTO relief was advocated as initial results had demonstrated that residual RVOTO was predictive of early mortality.[5] This approach resulted in relatively good long-term survival.[6] However, residual lesions after repair were common and follow-up studies of these first operations showed that these residual lesions resulted in late morbidity and mortality.[7-10] Pulmonary regurgitation (PR) was reported in the majority of patients, more commonly in those with TAPs.[11] PR initially was thought to be a relatively benign hemodynamic residual lesion but subsequently was found to be predictive of decreased exercise performance and progressive RV dilation. RV dilation, in turn, was associated with ventricular arrhythmia and biventricular dysfunction.[12-14] Furthermore, patients were noted to be at higher risk of sudden cardiac death.[7, 8, 10, 15, 16]

Different surgical techniques were developed minimizing the extent of the ventriculotomy and trying to preserve competence of the pulmonary valve without causing significant residual RVOTO. Via a transatrial or transatrial-transpulmonary approach, the need for a ventriculotomy can be reduced (Figure 2, right). The transatrial or transatrial-transpulmonary approach is currently employed in most centers, and the long-term results are excellent.[11, 17-20] In patients with a small pulmonary valve annulus, a TAP is still necessary for adequate RVOTO relief. Other techniques to preserve or replace pulmonary valve competence include pulmonary valvuloplasty with patching limited to the infundibulum,[21, 22] implantation of a monocusp valve,[23, 24] a valved RV-to-PA conduit, [25, 26] or a homograft valve.[25] A survival benefit of these valve-sparing or valve-replacing techniques has not yet been demonstrated.[27-30]

Figure 2. Transventricular (left) and transatrial-transpulmonary (right) approach to Tetralogy of Fallot (ToF) repair



VSD, ventricular septal defect. Adapted from Bushman[175] with permission from the publisher.

Variations in current treatment strategies

In general, it is thought that earlier primary repair of ToF can limit prolonged exposure to RV pressure loading and reduced oxygen saturations, preserving cardiovascular[31] and brain[32] function. However, there is no consensus on the definition of "early" versus later repair. Neonatal repair (that is, repair before 1 month of age) is feasible with acceptable results but is not widely used and this is because of better short-term outcomes of non-neonatal repair.[33] Neonatal repair more often requires TAP compared with repair beyond the neonatal period, resulting in worse event-free survival.[33] In the majority of patients, primary repair can be postponed to 3 to 6 months of age with excellent outcomes.[34, 35]

Symptomatic ToF patients may require an intervention in the neonatal period. Different strategies can be used if primary repair is judged not to be the best option. Historically, a systemic-to-pulmonary shunt — typically a modified Blalock-Taussig (mBT) shunt — has been used to increase pulmonary flow, reduce hypoxemia, and allow time for PA growth. This allows repair to be performed at an older age and has the potential advantage of using no, or less extensive, TAP. However, palliative shunt procedures are associated with a 3% to 5% early mortality rate.[36, 37] The superiority of a staged approach versus primary neonatal repair has not been demonstrated.[38, 39]

Stenting of the ductus arteriosus (DA) is another strategy to warrant pulmonary blood flow after birth by inducing a systemic-to-pulmonary shunt. However, in cyanotic CHD, the anatomy of the DA might be complex and unsuited for stenting.[40] Procedural success is estimated to be 83%.[41] Recently published multicenter studies compared outcomes following DA stenting and mBT shunting using propensity score–adjusted models.[41, 42] Clinical status, assessed by saturation, hemoglobin levels, and PA size, was more favorable following DA stenting compared with mBT shunting.[41, 42] Bentham *et al*. found better survival (hazard ratio 0.25, 95% confidence interval (CI) 0.07–0.85) for DA stent compared with mBT,[41] whereas Glatz *et al*. found no difference in survival (hazard ratio 0.64, 95% CI 0.28–1.47).[42] A trend toward higher re-intervention rate in the DA stent group was observed in both studies.[41, 42] DA stenting appears to be a feasible strategy for selected cases.

Alternatively, palliative balloon dilation of the pulmonary annulus can be used to increase oxygen saturation and promote growth of the pulmonary vasculature and as bridge to later complete repair in selected patients.[43, 44] Whether this strategy ultimately reduces TAP use or improves long-term outcomes remains controversial.[43, 44]

Similarly, RVOT stenting can be used as a palliative strategy or bridge to repair in neonatal life.[45, 46] Experience with this strategy is still relatively limited but it has been demonstrated to be a relatively safe procedure promoting growth of the pulmonary arteries as a bridge to repair.[46-48] Quandt *et al*. compared medium-term outcomes of RVOT stent with systemic-to-pulmonary shunt and found no difference in survival between strategies.[47] Intensive care and hospital stay duration and peri-operative complications were more favorable for the RVOT stenting group but the re-intervention rate was higher for this group.[47] The most common re-interventions in this group were

re-stenting and re-ballooning. (Re)shunt surgery or early complete repair was less common in this group compared with patients who underwent primary mBT. Comparisons between neonatal repair and RVOT stenting have shown comparable short-term and long-term outcomes.[49, 50] During 10 years of follow-up, Wilder *et al*. demonstrated a similar increased rate of catheter-based re-interventions in the RVOT stent group compared with neonatal repair.[50] More studies are needed to determine the best strategy for the patient group requiring early intervention. Management strategies likely need to be individualized for optimal outcome.

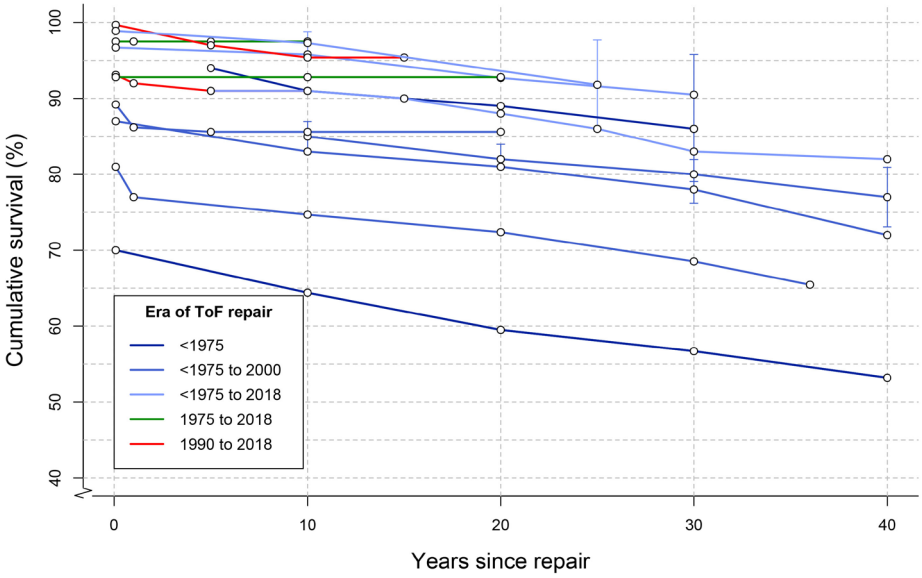
Overall survival

Overall survival following ToF repair has significantly improved in recent eras. Figure 3 outlines survival in several large studies published within the last two decades, and follow-up was up to 40 years for older cohorts.[11, 51-63] Early mortality has significantly decreased in more recent eras. European and American congenital cardiothoracic surgery registries have reported a peri-operative mortality below 3% in recent years.[64-66] Peri-operative outcomes are determined largely by the severity of the ToF described by, for example, the pre-operative size of the pulmonary valve and pulmonary arteries, RV-PA pressure gradient, and oxygen saturation.[59, 67-69] Patients with repair including TAP have higher peri-operative mortality.[64] As most centers consider a TAP only when the pulmonary annulus z-score is lower than −2 or −3, this in part reflects more severe ToF.[19, 70] Furthermore, co-morbidities, such as coronary abnormalities, prematurity, small body size–associated lesions, and genetic abnormalities, have been associated with increased peri-operative mortality.[59, 67-69, 71]

Mortality rates at medium-term follow-up have not changed much across the different surgical eras (Figure 3).[63] Survival at 30 years ranges from 68.5% to 90.5%.[52, 55, 56, 60-63] Long-term (20 to 30 years) survival from large cohorts of patients operated on with more recent surgical modifications of ToF repair (for example, valve-sparing and valve-replacing techniques) is still lacking. Important factors determining long-term outcome are residual RVOTO and severity of PR.[52]

Survival into adulthood is currently expected following ToF repair, leading to a growing population of adults with corrected ToF who require lifelong specialized medical care.[72-75] Re-interventions are common in these patients. Cuypers *et al*. found that 44% of patients underwent at least one surgical or catheter re-intervention after 35 years of follow-up.[61] D'Udekem *et al*. found that 24 ± 5% of patients underwent re-operation after 30 years of follow-up.[62] Following transatrial transpulmonary repair, lower rates of re-interventions have been reported. Luijten *et al*.[11] found a 80% freedom of re-intervention and death after 10 years and D'Udekem *et al*.[62] found 75% freedom of re-operation after 25 years.[11, 62] A small case-control study found a lower pulmonary valve replacement (PVR) rate following transatrial repair compared with transventricular repair. The use of a TAP is associated with a higher re-intervention rate,[11, 52] as is severity of ToF at repair.[54, 63] Specific indications for re-interventions will be discussed later in this article.

Figure 3. Survival following Tetralogy of Fallot (ToF) repair



Each colored line represents a single study, and dots represent Kaplan–Meier survival estimates at different time points.[11, 51-63] Ninety-five percent confidence intervals, where published, are shown in vertical lines. Lines are colored according to surgical era.

Residual problems and re-interventions

Residual right ventricle outflow tract obstruction

Residual RVOTO is common following repair and results in residual or progressive concentric hypertrophy of the RV. Data obtained from the INDICATOR study suggest that RV hypertrophy, due to increased mass-to-volume ratio, is a more important long-term risk factor for ventricular tachycardia (VT) and death than severity of RV dilation (RV end-diastolic volume index).[76] Current guidelines provide clear indications for re-intervention for residual RVOTO (Table 1).[73-75] Balloon valvuloplasty or PVR can be performed for valvular pulmonary stenosis (PS). PA branch stenosis can be safely relieved by balloon dilation, stenting, or PA reconstruction.[77] In several large studies, 1% to 7% of patients have undergone PA dilation or stenting at long-term follow-up (median of 5.8 to 36 years).[59, 61, 62, 78, 79] Surgical relief of the RVOT and PA plasties were performed in 1% to 5% of patients at long-term follow-up.[59, 61, 78, 79]

Pulmonary regurgitation

PR is very common at medium- to long-term follow-up. Five to ten years after repair, 40% to 85% of patients have moderate to severe PR.[51, 71, 80-82] PR induces RV volume overload of the RV with often progressive RV dilation, which may include the development of tricuspid regurgitation (TR) and RV dysfunction. It is often accompanied

by prolongation of the QRS complex, and RV dyssynchrony could contribute to the progression of dysfunction.[83-85] There generally is a long period in a compensated state, during which RV function is maintained. In some patients, these compensatory mechanisms fail, leading to progressive RV dysfunction.[83, 84] The mechanisms of RV adaptation and remodeling, as well as the molecular events contributing to the transition from a compensated to a decompensated state, are still poorly understood. Timely restoration of pulmonary valve competence is considered to halt the progressive adverse RV remodeling resulting in RV dysfunction seen in chronic PR.

Table 1. Indications for pulmonary valve replacement in current guidelines

	European Society of Cardiology (2010)[75]	**American College of Cardiology/American Heart Association (2008)**[73]	**Canadian Cardiovascular Society (2009)**[74]
Class I	Symptomatic patients with severe PR and/or PS (RV systolic pressure >60 mm Hg, TR velocity >3.5 m/s)	Severe PR and Symptoms or decreased exercise tolerance	
Class IIa	Severe PR or PS (or both) and either:	Severe PR and either:	Free PR and either:
RV size		Moderate to severe RV enlargement	EDVi 170 mL/m^2
Progression of RV size	Progressive RV dilation		Progressive RV dilation
RV function	Progressive RV dysfunction	Moderate to severe RV dysfunction	Moderate to severe RV dysfunction
TR	Progressive TR, at least moderate	Moderate to severe TR	Important TR
PS	PS RV systolic pressure greater than 80 mm Hg, TR velocity 4.3 m/s	Peak instantaneous echocardiography gradient greater than 50 mm Hg or RV/LV pressure ratio greater than 0.7 or Residual RVOT obstruction (valvular or subvalvular) with progressive and/or severe dilatation of the RV with dysfunction	RV pressure at least 2/3 systemic pressure
Exercise capacity	Decrease in objective exercise capacity		Symptoms such as deteriorating exercise performance
Arrhythmia	Sustained atrial or ventricular arrhythmia	Symptomatic or sustained atrial and/or ventricular arrhythmias	Atrial or ventricular arrhythmia

Abbreviations: EDVi, end-diastolic volume index; LV, left ventricle; PR, pulmonary regurgitation; PS, pulmonary stenosis; RV, right ventricle; RVOT, right ventricle outflow tract; TR, tricuspid regurgitation.

Thirty-five years after ToF repair, PVR will have been performed in about 40% of patients.[61, 63, 86] Staged repair and TAP are risk factors for late PVR.[11, 52, 61, 78], whereas mild residual PS seems to reduce risk.[87] As more patients with ToF survive into adulthood, PVRs are increasingly being performed.[88]

PVR is effective in decreasing RV volumes, reducing TR, decreasing QRS duration, increasing left ventricle (LV) ejection fraction (EF), and improving functional status.[89, 90] It should be noted that no improvement in survival following PVR compared with medical management has been demonstrated to date.[91, 92]

Homograft or bioprosthetic valves are currently the preferred valves for PVR.[93] The current 10-year re-PVR–free survival of ToF patients undergoing homograft PVR ranges from 74% to 89%.[93, 94]

Tissue-engineered valves with a non-synthetic and non-immunogenic surface have the potential to provide lifelong valve replacement.[95] *In situ* tissue engineering techniques, in which a decellularized "starter scaffold" of polymers can be used to provide shape and structure to the valve, are of particular interest. This scaffold is infiltrated by endogenous cells to provide a regenerating functional valve. As the scaffold would be non-immunogenic, this could provide a relatively cheap "off the shelf" valve. Current studies evaluating tissue-engineered valves in animals and humans show promising early results.[96]

Several transcatheter PVR strategies have been developed and are increasingly used in a clinical (trial) setting.[97] However, clinical experience compared with (surgical) homograft PVR is limited.[97] Procedural success of transcatheter PVR is generally good (>95%).[98] The hazard rate for re-intervention following transcatheter PVR ranges from 0.4% to 5.9% per patient-year.[98] However, high rates of infective endocarditis during follow-up have been described.[99] Recent results from the MELODY Registry estimate the infective endocarditis risk to be 2.3% per patient-year.[100] In comparison, the infective endocarditis risk in surgical PVR has been estimated to be 0.3% per patient-year.[101] Transcatheter PVR has been shown to increase exercise capacity and quality of life 6 months after the procedure.[102, 103] Direct comparisons with surgical PVR are still lacking.

Arrhythmia

Ventricular tachycardia

VT is a common arrhythmia in the repaired ToF population. Cuypers *et al*. reported a 5% cumulative incidence of sustained VT after a median of 35 years after ToF repair[61] and these figures are similar to those of most reports.[56, 104] However, cumulative incidences of up to 15% have been reported in some adult populations.[105] Predictors of sustained VT include higher age, number of prior cardiac surgeries, presence of a TAP, LV diastolic dysfunction, and QRS width.[61, 104-106] Most guidelines recommend implantable cardioverter defibrillators (ICDs) for patients who have had sustained VT or cardiac arrest.[74, 75] ICDs are also employed for primary prevention, although selecting high-risk patients who would benefit from ICD implantation remains challenging.[74, 75] Pacemaker and ICD prevalences in adult ToF populations both range from 5% to 10%.[61, 105, 107]

Electrophysiological studies can help to determine the underlying substrate, and radiofrequency ablation can be performed. Ablation of monomorphic VT substrates has excellent short-term outcomes with recurrent VT in 18% of patients after a mean follow-up of 34 months.[108] Another study found a similar recurrence rate (19%) 10 years after ablation.[109]

Supraventricular tachycardia

The prevalence or cumulative incidence of supraventricular tachycardia (SVT) in adult patients ranges from 4% to 20%.[105-107, 110] In the first 10 to 15 years following ToF repair, SVT is relatively uncommon but the incidence rises steadily after this period.[105] Intra-atrial re-entrant tachycardia, typically involving the right atrium, is the most common type of SVT in patients with ToF.[105] Two large studies found that SVT was an independent predictor of death or VT.[76] Few studies have assessed the efficacy of ablation of atrial arrhythmias in corrected ToF, and long-term follow-up is lacking.[111-113]

Aortopathy

Dilation of the aorta is seen in 12% to 24% of adult patients with ToF.[114-116] In patients with aortic dilation, aortic root size seems to progressively increase over a period of years. Aortic dissection following ToF appears to be a rare complication.[117] A population-based study in Texas demonstrated no increased risk for thoracic aortic dissection for patients with ToF compared with the general population.[117] However, progressive aortic root dilation can lead to malcoaptation of the aortic valve and aortic regurgitation. Furthermore, the elasticity of the dilated aortic root was shown to be reduced in patients with ToF, possibly hampering circulatory function.[118] The importance of aortopathy in circulatory function and mortality remains incompletely understood.

Knowledge gaps

Right ventricular adaptation and remodeling

The mechanisms of RV adaptation and remodeling in response to chronic RV volume overload, resulting from PR, are poorly understood.[119] In young pig models, chronic PR affects biventricular systolic function, RV myocardial contractility, and LV diastolic performance.[120] Histopathology of several animal models displays early hypertrophy of the chronically volume-loaded RV and, in a later stage, myocardial fibrosis.[119] The molecular responses to increased volume or pressure loading of the RV are different from those in the LV.[119, 121-123] In a pig model of repaired ToF with induced PR, PS, and an RVOT scar, RV hypertrophy and dilation were found after 23 weeks. The myocardium was characterized by increased collagen deposition, leading to decreased impulse conduction velocity and dispersion.[124] Similar findings were found in the LV, despite preserved LV function at this stage. This demonstrates biventricular adverse effects are present early in the adverse remodeling process.[125]

Basic research into RV remodeling has focused mainly on the response to increased pressure loading rather than the predominantly volume-loaded RV as seen in PR.[122, 123]

Volume loading and pressure loading increase myocardial metabolic demand. This metabolic stress induces an increased amount of reactive oxygen species. Compensatory anti-oxidant production in the RV is impaired compared with the LV.[123] This might imply that the RV is more vulnerable to oxidative stress, as seen in abnormal loading conditions.

In volume-loaded RV mouse models, a clinical course similar to RV dysfunction with volume-loaded RV in humans is observed. RV function is maintained during a compensated phase, followed by RV dysfunction.[126] Gene expression patterns of the cardiomyocyte in the compensated state differ from those of healthy controls. Several molecular pathways, such as transforming growth factor beta (TGF-β) signaling, p53 signaling, and cytoskeleton-related pathways are downregulated in the early compensated state but show late upregulation as the RV progressively remodels.[126] However, the exact cellular and molecular mechanisms of transition from a compensated to a decompensated state of the volume-loaded RV have not been fully elucidated.[123, 127]

Assessing the right ventricle in patients with Tetralogy of Fallot

Our limited understanding of the pathophysiology of RV failure hampers our ability to adequately detect failure in the early stages in clinical practice. Imaging techniques are used to assess the RV and follow patients serially, aiming to detect early changes in biventricular size and performance. Cardiovascular magnetic resonance (CMR) imaging is routinely used to reliably quantify RV volumes and function, wall mass, and PR.[128] Adverse clinical events have been related to larger RV volumes, PR severity, biventricular EF, and mass-to-volume ratio.[76, 129, 130] Increased RV volumes, most commonly end-diastolic volume index (EDVi), have been considered a sign of prolonged high PR burden and thus a predictor of RV dysfunction. However, exercise capacity can be preserved even in severely dilated ventricles, demonstrating that compensatory mechanisms can still be adequate to maintain performance of large RVs.[131] In the INDICATOR cohort, increased RV wall mass-to-volume ratio, among other factors, was found to be an independent predictor of VT and all-cause mortality, whereas RV EDV and end-systolic volume were not predictive of the end-points.[76] RV hypertrophy could be a more sensitive marker of pending dysfunction than EDV, although this might be particularly true for patients with residual PS.

Regional myocardial performance and mechanical synchrony can be assessed by strain imaging studies. Global circumferential or longitudinal strain has been used to assess RV function. Under normal circumstances, the RV ejects mainly by longitudinal shortening while, with increased RV pressure loading, circumferential contraction is increased.[132] The predictive value of global longitudinal or circumferential strain in ToF is still uncertain: Orwat *et al*. found that RV global longitudinal strain assessed by CMR was a superior independent predictor for death, cardiac arrest, or VT compared with RV volumes.[133] RV global circumferential strain was not predictive of outcome in that study.[133] Diller *et al*. found a similar relation for LV global longitudinal strain assessed by echocardiography.[134]

Mechanical dyssynchrony has been demonstrated to relate to prolonged or fragmented (QRS complex containing additional spikes without bundle branch block) QRS complexes.[135] The contributions of this mechano-electrical interaction to RV function remain uncertain, as studies assessing mechanical dyssynchrony report conflicting results.[133, 134, 136-139] RV circumferential dyssynchrony was shown to negatively predict exercise capacity in one study.[138] This association has not been confirmed in other studies.[139, 140] Cardiac resynchronization therapy is increasingly used in ToF. A recent study found that 12 out of 15 adult patients with ToF had an improved NYHA (New York Heart Association) class or LV function after 2.6 years (median) of cardiac resynchronization therapy.[141] Procedural success was high and adverse events were rare.

Right ventricular interactions in Tetralogy of Fallot

Atrio-ventricular interactions. Diastolic function after ToF repair is a determinant of the amount of PR. In some patients, end-diastolic forward flow (EDFF) in the main PA during right atrial contraction can be observed.[142] This is considered a sign of "restrictive RV physiology" as the non-compliant RV acts as a conduit during atrial contraction as RV diastolic pressure exceeds PA diastolic pressure.[143, 144] Restrictive physiology could limit the amount of PR as elevated diastolic RV pressure reduces the amount of PR. A recent study found no relationship between the presence of EDFF and other markers of diastolic dysfunction (that is, RV hypertrophy, atrial dilatation, reduced stroke volume, or reduced PR).[145] Different mechanisms, such as pulmonary arterial capacitance and atrial function,[146] may play significant roles in the occurrence of EDFF. Luijnenburg *et al*. found that bi-atrial function, but not diastolic ventricular function, differed between patients with EDFF and those without it.[146] In that study, abnormal atrial function was related to worse exercise capacity and higher N-terminal pro brain natriuretic peptide (NT-proBNP). Kutty *et al*. found that right atrial longitudinal strain predicted RV performance but not exercise capacity.[147]

The effect of EDFF on circulatory function is controversial. Studies found conflicting results regarding the relationship between EDFF and the amount of PR,[142, 143, 145] exercise capacity,[143-146] and EDV.[143-146] The presence of EDFF might have a different etiology and clinical importance early versus late after repair or in severely dilated versus non-dilated ventricles.

Ventriculo-arterial interactions. Adequate atrio-ventricular coupling and ventriculo-arterial (VA) coupling are required for an energetically efficient transfer of blood through the right heart. VA coupling has not been studied extensively in ToF. Latus *et al*. assessed VA coupling as the relationship between pulmonary arterial elastance and ventricular end-systolic elastance in adult patients with ToF by using CMR and catheter-derived measurements both in resting conditions and during dobutamine stress.[148] VA coupling was impaired during resting conditions. EF and load-independent parameters of RV contractility increased during dobutamine stress. Pulmonary arterial elastance

increased accordingly and the impaired VA coupling that resulted during dobutamine stress was similar to that under resting conditions.

Interventricular interactions. Interactions between the RV and LV have been extensively described. The LV and RV have common myocardial fibers, the interventricular septum, the anatomic space confined by the pericardium, and a common neurohumoral system.[149] Not unexpectedly, the effects of chronic PR are not limited to the RV, although the mechanisms of this ventriculo–ventriculo interaction in chronic PR remain poorly understood. A linear correlation between LV and RV EF has been described.[149, 150] Severe RV dilation causes abnormal diastolic septal positioning, influencing LV filling.[151] The role of the LV in outcomes in ToF is increasingly appreciated, as LV function has been associated with increased mortality and increased risk of VT.[134, 152] In the INDICATOR registry, LV EF was one of three independent predictors of mortality and VT.[153] Geva *et al*. found that LV EF, independent of RV parameters, predicted poor functional status.[150] Remarkably, parameters of LV function are not considered in current guidelines for the timing of PVR (Table 1).

Drug therapy for right ventricular failure

Pharmacotherapy is important in the treatment of LV failure and improves outcomes. However, the effects of the use of heart failure medication for RV failure have been disappointing.[154-156] In patients after ToF repair, RAAS (renin–angiotensin–aldosterone system) inhibitors do not appear to influence RV EF or exercise capacity.[157] In a randomized controlled trial of 33 patients with ToF, beta blockers showed no beneficial effects after 6 months of treatment and an increase in NT-proBNP was noted.[158] Increasing our understanding of the pathophysiology of RV failure might elucidate new targets for medical treatment unique to the RV.

Current guidelines on the timing of pulmonary valve replacement

Restoring pulmonary valve function before irreversible RV dysfunction occurs could be important to prevent RV failure. However, the durability of currently used pulmonary prosthetic valves is limited. Therefore, the timing of PVR always is a compromise: It should be timed early enough to prevent irreversible adverse remodeling but late enough to limit the number of re-interventions. Because of the difficulties in assessing RV function, predicting decline in RV function is difficult, and the optimal timing of PVR is controversial. Guidelines by the European Society of Cardiology, the Canadian Cardiovascular Society (CCS), and the American College of Cardiology/American Heart Association provide some recommendations on indications for performing PVR.[73-75] These indications are summarized in Table 1.

Indications differ between guidelines and have several limitations. Most guidelines do not provide specific cutoff points since these are statistical constructs that do not work for individual patients. The 2009 CCS guideline provides an absolute cutoff value for EDVi but does not take into account the considerable differences in normal (indexed)

RV volumes between genders and age.[159] End-systolic volume index and RV mass-to-volume ratio have been proposed as superior predictors compared with EDV.[76, 160] Progressive RV dilation is considered an indication for PVR, but there is no consensus on what too much progression is.[161-164] Longitudinal changes in RV size and function following ToF repair have been reported in several studies.[165-172] RV volumes increase non-linearly and seem to stabilize in adolescence. These factors need to be taken into account when assessing progressive RV dilation.

Furthermore, the recommendations in current guidelines are often based on long-term outcomes of studies in patients who have been operated at a much older age than has been the practice in the past 20 years. This warrants caution when extrapolating these results to current adolescent or younger patients.

Careful interpretation of current guidelines seems to be justified. Individual patient parameters and views should always be taken into consideration. In clinical practice, an approach using information from different sources, including history, physical examination, electrocardiogram, imaging techniques, exercise testing, and blood biomarkers, may be most useful.[173]

Conclusions

ToF can be repaired with low short-term and long-term mortality. This has caused a demographic shift such that many patients survive well into adulthood. Long-term follow-up of older cohorts has shown the detrimental effects of PR in the long-term. However, residual lesions cause significant morbidity. Surgical modifications to preserve pulmonary valve function, such as the transatrial (and transpulmonary) approaches and restricted use of TAPs, have been widely adopted. Despite improvements in morbidity, follow-up duration for these techniques is probably too limited to demonstrate a survival benefit.

Our limited understanding of RV adaptation and the pathophysiology of RV heart failure hampers the ability to detect failure in early stages in clinical practice and to predict future decline of RV function. While a large proportion of adult ToF survivors require one or multiple PVRs in their lifetimes, selecting optimal candidates and optimal timing for PVR remains challenging. Increasing our understanding of RV failure seems key to answer these difficult questions. This might provide treatment options to attain optimal long-term health outcomes for patients with ToF.

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Chapter 7

Longterm outcome of transatrial-transpulmonary repair of Tetralogy of Fallot

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Abstract

Objectives

The surgical approach to repair of Tetralogy of Fallot (ToF) has shifted over the years. We aimed to report the long-term follow-up after ToF repair with the transatrial–transpulmonary approach and to determine predictors of long-term outcomes.

Methods

Retrospective analysis of patients operated on in two tertiary referral centres. Primary outcome measures were: death, pulmonary valve replacement (PVR), reintervention for other reasons, internal cardiodefibrillator and/or pacemaker placement. Kaplan–Meier assessment of overall and event-free survival as well as uni- and multivariate analyses of risk factors for outcomes were performed.

Results

Four hundred and fifty-three patients were included. Median age at operation was: 0.6 years (range 0–19.6) and median age at the last follow-up was 14.3 years (range 0.1–42.1). Median age at repair decreased from 1.2 years (range 0.6–5.8) (1970–80) to 0.3 years (range 0–4.7) (2000–12). A transannular patch (TP) was used in 65% of all patients. The use of a TP showed a decline from 89% in the initial years of the cohort to 64% in 2000–12. Early mortality was 1.1% (5 patients) for the entire cohort and late mortality 2.4% (11 patients). Overall survival for the entire cohort was 97.3% (95% CI 95.7–98.8) and 91.8% (95% CI 85.9–97.7) at 10 and 25 years, respectively. For patients with a TP (n= 294) vs non-TP (n= 159), this was 97.2% (95% CI 95.2–99.2) vs 97.5% (95% CI 95.1–99.9) at 10-year and 91.0% (95% CI 83.9–98.1) vs 96.3% (95% CI 93.0–99.6) at 25-year follow-up (P= 0.958). Fifty-two patients underwent PVR, and in 5 a pacemaker was inserted. Event-free survival for TP versus non-TP patients was 80.2% (95 CI% 75.5–84.9) vs 81.7% (95% CI 75.2–88.2) at 10-year and 27.9% (95% CI 17.7–38.1) vs 78.5% (95% CI 71.4–85.6) at 25-year follow-up (P= 0.016). In multivariate analysis, both the use of a TP (HR 1.705, 95% CI 1.023–2.842) and the year of surgical repair of Tetralogy of Fallot (HR 1.039, 95% CI 1.006–1.073) were associated with a higher probability of an event.

Conclusions

ToF patients corrected with the transatrial–transpulmonary approach have good long-term survival. PVR is a frequent event at longer follow-up, and other events are limited. The use of a TP is a predictor for poorer event-free outcomes, increasing the risk of the composite endpoint 1.7 times.

Introduction

Surgical correction of Tetralogy of Fallot (ToF) is reported to date back as early as 1954. Since then major developments have resulted in excellent present-day survival in ToF patients, which is, however, still reduced compared to the overall population.[1]

Over the years the surgical approach to ToF has shifted from a repair via a right ventriculotomy, commonly combined with a patch in the right ventriculair outflow tract (RVOT), often after initial palliative shunting, to a transatrial-transpulmonary approach often as primary repair.[1] The aim of the latter approach was to minimize the unfavourable side effects associated with a ventriculotomy, such as transmural myocardial scarring and coronary artery damage, which were thought to contribute to long-term impairment of right ventricular function and the risk for ventricular arrhythmias.[2]

Long-term complications like decreased exercise intolerance, (right) heart failure, arrhythmias and sudden death are well-known to occur after repair of ToF.[2] Pulmonary valve replacement (PVR) and, to a lesser extent, implantable cardiodefibrillator (ICD) placement are common procedures long-term after repair of ToF.

Predictors for negative long-term outcome after ToF repair have been studied extensively and include the amount of residual pulmonary regurgitation (PR), right and left ventricular size and function, myocardial tissue composition, right ventricular outflow function and electrical inhomogeneity.[2-6] Despite extensive literature on the results of ToF repair, relatively limited information is available specifically on the long-term outcomes of the transatrial-transpulmonary approach. Many studies on the subject of long-term outcome of ToF repair have not focussed on the outcomes of this approach, have used different criteria to define the population with ToF that was included, or have been hampered by small patient numbers or short duration of follow-up.[7, 8]

The aims of this study were to report the long-term follow up after ToF repair with the transatrial-transpulmonary approach in a relatively large cohort and to determine predictors of long-term adverse outcome.

Patients and methods

Patients

A retrospective analysis was made of all patients that underwent ToF repair with a transatrial-transpulmonary approach in two tertiary referral centres in the Netherlands, with special attention to whether a transannular patch (TP) was used or not (non-TP). Data of all patients born after January 1st 1970 and who had undergone ToF repair were analysed. ToF was defined as ventricular septal defect with anterior deviation of the outflow septum, without major anomalies, requiring desobstruction of right ventricular outflow obstruction and closure of ventricular septal defect. Patients with

other diagnoses including pulmonary atresia (PA), double outlet right ventricle (DORV), atrioventricular septal defect (AVSD) and absent pulmonary valve syndrome (APVS) were excluded. Other exclusion criteria were patients whose surgical reports were not available, patients with insufficient follow-up data and patients who did not have a transatrial-transpulmonary ToF repair.

In general, in all the years of the study, the transatrial-transpulmonary strategy essentially consisted of right atriotomy as first step in the approach of the VSD and the RVOT. As second step the main pulmonary artery was opened with a longitudinal incision as an approach to the pulmonary valve and the subvalvular area. Only after endoventricular desobstruction of the RVOT and when considered necessary by the attending surgeon, this incision was continued along the length of the infundibulum and reconstructed with a TP to create an adequate diamater of the RVOT. Patients in whom primarily a ventriculotomy was performed were excluded from our study.

Patients were included if treated in the Erasmus Medical Centre (EMC), Rotterdam or the Radboud University Medical Centre Nijmegen (RadboudUMC), Nijmegen, the Netherlands.The study complies with the regulations of institutional review boards with regard to retrospective data collection.

Methods

Data collection

The medical and surgical records of all patients were reviewed. Demographic characteristics are given in Table 1. Characteristics of the ToF repair including operative techniques and preoperative parameters were collected (Table 2). Postoperative complications were scored.

Primary outcomes were defined as death, PVR, late reoperations other than PVR, balloon dilatations for pulmonary stenosis (PS) and the placement of an ICD or pacemaker. Patient status was checked in the municipal basic administration in the Netherlands. Patients lost to follow-up were censored at the last known follow-up date according to hospital records and / or the municipal basic administration. We recorded and analysed the last outpatient visits for all patients in the period from 1 January 2010 until 30 June 2012. Collected parameters were: length, weight, use of medication, QRS-duration and QTc-time (corrected QT-time) on ECG, severity of PR, PS and RV dilatation on echocardiography and VO_2 max, maximal work load and maximal heart rate at graded step-wise bicycle cardiopulmonary exercise testing. The presence of residual PS was recorded if a mean echocardiographic gradient of ≥16 mmHg was present. The severity of pulmonary and tricuspid regurgitation (TR) was assessed semi-quantitatively on echocardiography.[9] MRI data obtained in relation to the latest outpatient visit were recorded. MRI volumetric data was indexed to body surface area.

Table 1. Patient characteristics (demographic)

	Number of patients (n=453)
Male (n, %)	286 (63.1)
Mean duration of pregnancy (weeks)	(n=290) 38.54±2.70
Mean birth weight (kg)	(n=266) 2.98±0.75
Median time to diagnosis (days)	(n=333) 36.00 (0-3504)
Other cardiac anomalities (n, %)	436 (96.2)
ASD (n, %)	359 (82.3)
PDA (n, %)	89 (20.4)
Unicuspid pulmonary valve (n, %)	29 (6.7)
Bicuspid pulmonary valve (n, %)	228 (52.3)
Right aortic arch (n, %)	70 (16.1)
Aberrant coronary origin (n, %)	22 (5.0)
Previous palliative shunts (n, %)	58 (12.8)
Mean PS gradient before repair (mmHg)	74±25 (n=224)

Data are either mean ±SD or median with range.

Abbreviations; ASD: atrial septal defect, PDA: patent ductus arteriosus, PS: pulmonary stenosis.

Complications after ToF repair were defined as infection, arrhythmia, early reoperation (within 30 days of complete repair) , fluid retention and prolonged use of inotropic drugs (>48hr)

Data analysis

Statistical analyses were performed with IBM SPSS Statistics 20 (SPSS, Inc., USA). We tested with a significance level of 0.05.

Data were summarized for all patients using frequencies and percentages for categorical variables and either mean ± standard deviation (SD) or median with range for numerical variables.

A student's t-test was used to compare means between independent groups. In case a value did not have a normal distribution, we calculated the medians and used a (non-parametric) Mann-Whitney test to compare these medians between the groups. We used a χ^2 test to compare categorical variables with a normal distribution between independent subgroups. When a categorical value was not distributed normally, Fisher exact test was used to compare these variables between groups. Chi-squared approximation was not considered suitable when the expected values in any of the cells of a table are below 5.

The probability of long-term survival and event-free survival was estimated by Kaplan-Meier curves. A log-rank test was used to compare these curves between different groups.

Table 2. Characteristics of TOF repair

	All Patients	TOFr between 1970-1980	TOFr between 1980-1990[1]	TOFr between 1990-2000[2]	TOFr between 2000-2012[3]	P-value[1-2]	P-value [2-3]
Number of patients	453	9	72	165	207		
Median age at repair (years)	0.58 (0.19-58)	1.17 (0.58-5.75)	1.58 (0.08-9.75)	0.75 (0-19.58)	0.33 (0-4.67)	<0.001	<0.001
Transpulmonary approach (n, %)	429 (94.7)	9 (100.0)	72 (100.0)	158 (95.8)	190 (91.8)	0.105	0.122
Valvulotomy (n, %)	177/450 (39.3)	0 (0.0)	23 (31.9)	80 (48.5)	74 (36.3)	0.018	0.018
Transannular patch (n, %)	294 (64.9)	8 (88.9)	56 (77.8)	98 (59.4)	132 (63.8)	0.006	0.388
Reoperation within 30 days of TOF (n, %)	20 (4.4)	1 (11.1)	9 (12.5)	6 (3.6)	4 (1.9)	0.017	0.349

We used either mean ±SD or median with range for numerical variables.
[1-2]p-value for comparison of the groups between 1980-1990 and 1990-2000.
[2-3]p-value for comparison of the groups between 1990-2000 and 2000-2012.
Abbreviations; ToFr: surgical repair of Tetralogy of Fallot.

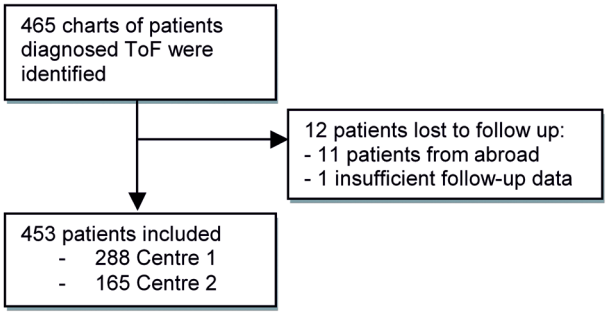
With a Cox proportional hazard analysis (forward step-wise regression method) we analysed whether parameters had an influence on the probability of an event. The seven best parameters in univariate analysis were included in the multivariate analysis. We composed a composite endpoint, which was defined as death, PVR, other (late: after 30 days after complete repair) reoperations, balloon dilatations for PS or pacemaker insertion.

Results

Patient characteristics

We identified 465 patients who met the inclusion criteria, as shown in Figure 1; 288 patients from Centre 1 and 165 patients from Centre 2 were included. Twelve patients were excluded because they were lost to follow-up. Eleven patients had their ToF repair in the Netherlands but lived abroad and were lost to follow-up. In 1 patient, the follow-up was insufficient.

Figure 1. Flow-chart of patient enrolment



Abbreviation; ToF: Tetralogy of Fallot.

Table 1 summarizes patient characteristics of the 453 patients; 63.1 % was male. In 96.2% of the patients associated cardiac anomalies were found: secundum type atrial septal defect in 82.3%, patent ductus arteriosus in 20.4%, uni- and bicuspid pulmonary valve in respectively 6.7% and 52.3%. A coronary artery had an aberrant origin in 5% of the patients an 16.1% had an right aortic arch.

Prior to TOF repair 12.8% of the patients received a palliative shunt, as shown in Table 1. This percentage was significantly higher in the patients who later received a TP compared with those who did not (15% (n= 45) versus 8 % (n= 13) (p=0.030). Mean PS gradient before complete repair was higher in the TP group compared to the non-TP group (80±24 (n= 134) vs 66±25 (n= 90) mm Hg (p< 0.001). The median age at repair

of ToF was 0.6 (0-19.6) years, as shown in Table 2. Of the 453 patients, a TP was used in 215 (47.5%) patients, and both a TP and valvotomy were done in 79 (17.4%). In further analysis these 294 patients were termed the TP group. In 98 (21.6%) patients, only pulmonary valvotomy was performed, and in 61 (13.5%) patients no valvotomy and no TP were required. These patients were included as the not-TP group (n= 159).

A total of 20 patients received an early reoperation within 30 days of ToF repair, as shown in Table 2. Eleven patients needed rethoracotomy due to rebleeding, 7 due to a residual VSD and 2 because of residual RVOT obstruction.

A trend towards decreasing median age at ToF repair over time was noted: in the cohort 1970-1980 median age at repair was 1.8 (0.6–5.8) years, compared with 0.3 (0–4.7) years in the cohort 2000-12. Valvulotomy increased during the years from 0.0% in the cohort 1970-1980 to 48.5% in the cohort 1990-2000, with a slight decrease in the cohort 2000-12 to 36.3%. The use of a TP shows a reverse trend: it decreased from 88.9% in the first cohort to 59.4% in the cohort 1990-2000, with a slight increase in the last cohort to 63.8%.

A total of 77 patients (17.0%) were diagnosed with a genetic syndrome or association. In 28 patients this concerned trisomy 21, in 25 patients 22q11 deletion, in 7 patients vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula and/or esophageal atresia, renal & radial anomalies and limb defects (VACTERL) association and in 17 patients a range of individual gene abnormalities, syndromes or associations.

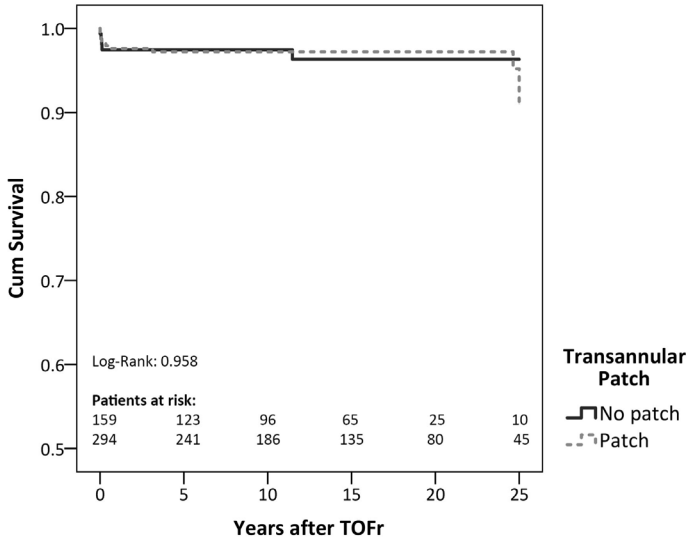
Survival and event-free survival

Sixteen patients died during follow up. This represents 3.5% of the study population. Early mortality (within 30 days of ToF repair) was 1.1% (5 patients), late mortality was 2.4% (11 patients). The median age at time of death was 1.8 (0.1–32.8) years. Eight patients died from cardiac causes, 6 from non-cardiac causes and in 2 patients the cause of death was unknown. Down-syndrome was diagnosed in 3 of the deceased patients, 2 deceased patients had the VACTERL-association.

The cumulative overall survival was 97.3% (95% CI 95.7–98.8) at 10 years and 91.8% (95% CI 85.9–97.7) at 25 years after ToF repair. Figure 2 shows the cumulative overall survival for patients with and those without a TP. Survival for the TP group was 97.2% (95% CI 95.2–99.2) at 10 years and 91.0% (95% CI 83.9–98.1) at 25 years after ToF repair, compared with 97.5% (95% CI 95.1-99.9) at 10 years and 96.3% (95% CI 93.0–99.6) at 25 years in the non-TP group (p=0.958).

The cumulative overall event-free survival was 80.7% (95% CI 76.9–84.6) at 10 years and 37.0% (95% CI 27.2–46.8) at 25 years after ToF repair. In Figure 3 the event-free survival is shown for the patients with and those without a TP. For the TP-group the cumulative total event-free survival is 80.2% (95% CI 75.5–84.9) at 10 years and 27.6% (95% CI 17.7–38.1) at 25 years; for the non-TP group it is 81.7% (95% CI: 75.2–88.2) at 10 years and 78.5% (95% CI 71.4–85.6) at 25 years after ToF repair. The differences in event-free survival were statistically significantly different (p=0.016).

Figure 2. Kaplan Meyer curve for overall survival



Abbreviation; ToFr: Tetralogy of Fallot repair.

Long-term outcomes

In Table 3, the long-term outcomes of all patients are shown. The patients are divided into two groups: TP (n= 294) and non-TP (n= 159). The median age at the end of the follow-up period for the entire cohort is 14.4 (0.1–42.1) years. There was no significant difference between the median age at the end of follow-up between the two subgroups.

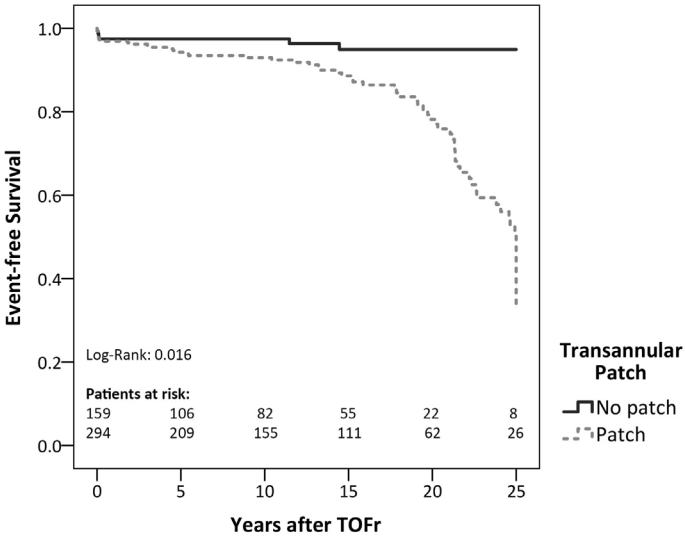
A total of 52 patients underwent a first PVR; this was 11.5% of the study population. The first PVR was performed at a median of 20.2 (1.9–34.8) years after the ToF repair. In the TP group, 51 (17.3%) patients received a PVR, and in the non-TP group only 1 patient (0.6%) did (p< 0.001).

As shown in Table 3, a total of 72 (15.9%) patients needed a late reoperation other than PVR, 17.0% in the TP group and 13.8% in the non-TP goup (p= not significant). Reoperations performed were infundibulectom (desobstruction of the RVOT) combined with reconstruction of the pulmonary artery in 3.3% of all patients. Isolated infundibulectomy (RVOT desobstruction) was performed in 4.9% of all patients and isolated reconstruction of the pulmonary was performed in 1.8% of all patients.

Clinical state at latest evaluation

In Table 4, information regarding the last outpatient visit between 2010 and 2012 is given. Three hundred and sixty patients were seen in that setting in this period, 49 of whom had had a PVR.

Figure 3. Kaplan-Meyer curve for event-free survival.



Abbreviation; ToFr: Tetralogy of Fallot repair.

Patients in the PVR group were significantly older than those in the non-PVR group: 27.7 (10.9–42.1) compared with 11.7 (0.3– 36.1) years (p< 0.001). The median age at follow-up post-ToF repair was also significantly higher in the PVR group.

Electrocardiography was performed in 341 patients and QRS duration was assessed in 324 patients. A significant difference (p< 0.001) was found in mean QRS duration between the two groups. In the PVR group, the mean QRS duration was 136 ± 25 ms, compared with 119 ± 25 ms in the non-PVR group. The mean QRS duration in all patients was 121 ± 26 after a mean follow-up of 12 years, and 5 patients had a QRS duration of more than 180 ms.

In 298 patients, an echocardiogram was performed. Seventeen percent of patients had no RV dilatation; mild dilatation was found in 32% of patients, moderate dilatation in 48% and severe dilatation in 2%. Echocardiography did not show statistically significant differences for RV size between the TP and non-TP groups.

A more than minimal residual PS gradient was found in 70% of the patients. Patients in the PVR group had significantly more PS than those in the non-PVR group: 90.0% compared with 66.2% (p=0.009).

In 246 patients, TR was noted at echocardiography. No TR was found in 21.5% of the patients, mild TR in 67.4% and moderate TR in 10.6%. In 0.4% of the patients, severe TR was found. Two patients with moderate TR underwent a PVR and the patient with severe TR had a pacemaker due to a third-degree heart block.

Table 3. Outcomes all patients with or without a transannular patch

	Patients (n=453)	Transannular patch (n=294)	No transannular patch (n=159)	p-value
Median age at end follow-up (years)	14.35 (0.09-42.13)	14.73 (0.09-42.13)	13.69 (0.24-35.05)	0.451
Median time after TOFr (years)	13.31 (0.00-36.31)	14.06 (0.00-36.31)	12.59 (0.00-33.87)	0.342
Patients with follow up >15 years	200	135	65	
Patients with follow up >20 years	105	80	25	
Patients with follow up >25 years	55	45	10	
1st PVR (n, %)	52 (11.5)	51 (17.3)	1 (0.6)	<0.001
Median follow-up after repair (years)	20.18 (1.93- 34.78)	20.25 (1.93-34.78)	14.45	-
1st PVR (n, %)	52 (11.5)	51 (17.3)	1 (0.6)	<0.001
Median follow-up after repair (years)	20.18 (1.93-34.78)	20.25 (1.93-34.78)	14.45	-
2nd PVR (n, %)	3 (0.7)	3 (1.0)	0 (0.0)	0.555
Pacemaker (n, %)	5 (1.1)	5 (1.7)	0 (0.0)	0.167
Balloon dilatation for PS (n, %)	32 (7.1)	24 (8.2)	8 (5.0)	0.214
Median follow up after repair (years)	2.64 (0.39-27.37)	2.52 (0.79-27.37)	3.11 (0.39-8.16)	0.683
Re-operations other than PVR (n, %)	72 (15.9)	50 (17.0)	22 (13.8)	0.378
Median follow up after repair (years)	1.42 (0-18.87)	1.20 (0-18.87)	2.42 (0-11.92)	0.443
Infundibulectomy and reconstruction pulmonary artery	15 (3.3)	7 (2.4)	8 (5.0)	0.132
Infundibulectomy	22 (4.9)	15 (5.1)	7 (4.4)	0.741
Reconstruction pulmonary artery	8 (1.8)	5 (1.7)	3 (1.9)	-
Died during follow-up (n, %)	16 (3.5)	11 (3.7)	5 (3.1)	0.937
Median age at time of death (months)	20.50 (1-394)	25.00 (1-394)	5.00 (2-152)	-

We used either mean ± SD or median with range for numerical variables.
Abbreviations: PVR: pulmonary valve replacement; ToFr: surgical repair of Tetralogy of Falllot.

Table 4. Clinical state at latest evaluation

	Patients (n=360)	Non PVR group (n=311)	PVR-group (n=49)	P-value
Median age (years)	13.68 (0.27-42.13)	11.70 (0.27-36.14)	27.77 (10.86-42.13)	<0.001
Adults (n, %)	106 (29.4)	65 (20.9)	41 (83.7)	<0.001
Mean BMI adults	(n=80) 23.28±4.20	(n=52) 23.43±4.47	(n=28) 23.00±3.73	0.668
BMI >25 (n, %)	21 (26.2)	14 (26.9)	7 (25.0)	0.852
Current medication use (n, %)	11/339 (3.2)	5/295 (1.7)	6/44 (13.6)	0.001
Median follow up age post correction (years)	12.00 (0-35)	10.00 (0-33)	24.00 (9-35)	<0.001
post 1st PVR (years)			3.00 (0-19)	
Electrocardiography data (n, %)	341	295	46	
Mean QRS duration (msec)	(n=324) 121.08±25.85	(n=278) 118.56±25.07	(n=46) 136.28±25.49	<0.001
QRS >180 msec (n, %)	5 (1.5)	3 (1.1)	2 (4.3)	0.149
Mean QTc time (msec)	(n=275) 425.46±34.18	(n=229) 426.86±35.01	(n=46) 418.52±29.08	0.132
Echocardiographic data (n, %)	298	261	37	
PR (n)	276	242	34	
No PR (n, %)	10 (3.6)	7 (2.9)	3 (8.8)	0.112
Mild PR (n, %)	74 (26.8)	52 (21.5)	22 (64.7)	<0.001
Moderate PR (n, %)	120 (43.5)	111 (45.9)	9 (26.5)	0.033*
Severe PR (n, %)	72 (26.1)	72 (29.8)	0 (0.0)	<0.001
RV dilatation (n, %)	216	189	27	
No dilatation (n, %)	37 (17.1)	34 (18.0)	3 (11.1)	0.584
Mild dilatation (n, %)	70 (32.4)	61 (32.3)	9 (33.3)	0.912
Moderate dilatation (n, %)	104 (48.1)	89 (47.1)	15 (55.6)	0.410
Severe dilatation (n, %)	5 (2.3)	5 (2.6)	0 (0.0)	-

Tricuspid regurgitation (n, %)	193/246 (78.5)	161/210 (76.7)	32/36 (88.9)	0.099
PS ≥16mmHg (n, %)	129/184 (70.1)	102/154 (66.2)	27/30 (90.0)	0.009
Ergometry (n)	58	47	11	
Mean % of predicted max VO_2	(n=34) 87.82±17.61	(n=28) 89.43±17.98	(n=6) 80.33±14.84	0.257
Mean % of predicted max watt	(n=50) 88.56±16.25	(n=40) 88.88±16.54	(n=10) 87.30±15.80	0.787
Mean max HF	(n=51) 174.45±17.32	(n=41) 175.61±17.04	(n=10) 169.70±18.54	0.338
MRI (n)	49	42	7	
Mean LV EDV (ml/m^2)	82.98±14.18	82.54±13.31	85.43±19.43	0.625
ESV (ml/m^2)	36.07±11.16	35.28±11.38	40.43±9.40	0.266
SV (ml/m^2)	47.52±9.04	47.97±8.60	45.00±11.66	0.429
EF (n, %)	57.47±7.96	58.26±8.21	52.71±3.86	0.088
Mean RV EDV (ml/m^2)	131.04±37.04	131.82±35.11	126.71±49.56	0.741
ESV (ml/m^2)	68.57±26.57	67.28±24.26	75.71±38.69	0.446
SV (ml/m^2)	62.72±17.33	64.82±17.48	51.00±11.42	0.051
EF (n, %)	49.45±8.13	50.67±7.71	42.14±7.06	0.009
PI (n, %)	32.73±16.95	33.00±14.59	(n=3) 29.33±42.34	0.895

We used either mean ±SD or median with range for numerical variables.
Abbreviations; BMI: body mass index, ESV: end-systolic volume; HF: heart frequency; LV EDV: left ventricle end-diastolic volume; PI: pulmonary insufficiency, PR: pulmonary regurgitation; PS: pulmonary stenosis; PVR: pulmonary valve replacement; RV: right ventricle; RV EDV: right ventricular end-diastolic volume; SV: stroke volume; QTc: corrected QT-time; VO_2: maximal oxygen consumption.

Predictors for negative outcome

Table 5 presents the results of Cox proportional hazard analysis of the most important parameters for the combined event. Univariate analysis showed that the use of a TP during ToF repair was associated with a higher probability of an event (HR 1.631, 95% CI 1.077–2.471). Also, postoperative complications after ToF repair (HR 1.506, 95% CI 1.035–2.191), year of TOFr (HR 1.034, 95% CI 1.007–1.061) and age at TOFr (HR 0.987, 95% CI 0.976–0.997) were associated with a higher risk. The parameters Hb level before ToF repair, male gender and the presence of a genetic disorder did not show a significant association in univariate analysis.

In multivariate analysis, both the use of a TP (HR 1.705, 95% CI 1.023–2.842) and year of TOFr (HR 1.039, 95% CI 1.006–1.073) were associated with a higher probability of an event.

In hazard analysis for the event death, both uni- and multivariate analyses did not show significant associations.

Table 5. Cox-regression combined event

	Univariate		Multivariate	
	HR	**95% CI**	**HR**	**95% CI**
Transannular patch	1.631*	1.077-2.471	1.705*	1.023-2.842
Complications after TOFr	1.506*	1.035-2.191	-	-
Year of TOFr	1.034*	1.007-1.061	1.039*	1.006-1.073
Hb level before TOFr	1.013	0.930-1.103	-	-
Age at TOFr (months)	0.987*	0.976-0.997	-	-
Gender	0.873	0.611-1.247	-	-
Genetic disorder	0.800	0.480-1.334	-	-

*Statistically significant factor with P-value < 0.05.
Abbreviation; ToFr: Tetralogy of Fallot repair.

Discussion

This study shows that overall, ToF patients corrected with the transatrial–transpulmonary approach have excellent survival rates. Over several decades, the operative mortality (5 of 453 patients) was 1.1%, and 25-year overall survival rate was 92%, more specifically 91% in the TP group and 96% in the non-TP group. In the time-span we studied, there was a clear trend towards repair at younger age and a decrease in the use of transannular patching of the RVOT, confirming other reports on this subject.

Whereas 10- to 15-year survival has been documented frequently in various cohorts of ToF, relatively few studies have reported on 25-year survival after ToF repair. In

2008, a group from Toronto reported a 25-year survival of ≈90% for ToF without PA, DORV, AVSD or branch PS, in patients born before 1984.[10] Recently, 25-year overall survival in a large Korean cohort was reported to be 93%, with statistically better survival for transatrial and non-transannular approaches.[11] The improvements in survival, in part, relate to improved early mortality.[10] While long-term deterioration of clinical state and the need for reinterventions are commonly recognized, it is less clear whether the mortality risk increases with time.[10] Considering the low rate of late mortality in our patients, this could not be assessed from our data. Of note, only 3.5% of the patients died, many of whom had associated genetic abnormalities. Most of these patients were relatively young at time of death. The number of patients who died late in follow-up in our cohort is very low. The explanation probably lies in the fact that with the surgical approach as described, these patients are in good clinical condition after ToF repair and apparently have a good prognosis with regard to survival for the observed period.[6, 12]

Timely reintervention is another factor to consider. In fact, there is a clear increase of reinterventions with time, particularly after 15-year follow-up. There was a clear difference in event-free survival for the TP versus the non-TP group. Multivariate analysis demonstrated that the use of a TP in the setting of transatrial– transpulmonary approach was associated with a 1.7 times higher risk of the composite endpoint of death, PVR, reoperation for other reasons, balloon dilatation for PS or pacemaker placement in our patients. This confirms findings from earlier reports in combined cohorts.[2] Since the use of a TP depends on the anatomy and haemodynamics at initial repair and often cannot be avoided, this emphasizes the importance of comparison of results among clearly defined and highly comparable populations.[5, 10, 13]

Event-free survival differs significantly from overall survival in most series. The majority of reinterventions are related to the long-term effects of PR and particularly consist of PVR. At a median follow-up of 15 years, 17% of our patients who had transannular patching of their RVOT at the initial repair had PVR; this compares favourably with similar reports in the literature.[10, 11] Patients without a TP had better event-free survival. These types of observations resulted in attempts to avoid transannular patching and avoid damage[1-24] to the pulmonary valve and/or infundibulum.[1, 8]

Recently, Bove et al.[8] demonstrated in an experimental setting that of the available alternatives, extensive transannular patching results in the most severely dilated and functionally impaired right ventricles. Whether the alternative TP-avoiding strategies will result in improved (event-free) survival of patients is to be seen; in earlier studies, this could not be demonstrated.[5, 8] The trade-off of restrictive strategies aimed to avoid residual PR may be an increased reoperation rate for residual stenosis. Preliminary data from a large registry study may point towards an increased risk of arrhythmias and sudden death in patients with residual RV outflow obstruction and RV hypertrophy.[17]

The long-term problems related to chronic PR are well known and include right ventricular dilatation, impaired right and left ventricular function and increased risk of

arrhythmias. Risk factors for late problems related to PR have been identified and include the amount of residual PR, right and left ventricular size and function, myocardial tissue composition, right ventricular infundibular and outflow tract function, right atrial function and electrical inhomogeneity.[2-5, 22] Many of these risk factors cannot be fully avoided, despite individualized operative strategies aimed at preservation of RVOT function.

A remarkable finding of our study is the lack of improvement in exercise performance, pro-arrhythmic ECG parameters, ventricular size and an increase in RVOT stenosis in patients after PVR. Although this data must be interpreted with caution considering the limited number of observations for some parameters, this questions the timing and effects of PVR. Considerable debate exists with regard to indications for PVR. Current guidelines include factors from history, ECG signs of increased electrical inhomogeneity and haemodynamic factors related to residual RVOT problems.[17] These factors include older age at repair and ECG parameters, particularly QRS duration. Recommendations with regard to RV size provide a wide range of end-diastolic dimensions, from ±140 to ±180 ml/m2 body surface area.[15, 16] In this size range of the RV, normalization of systolic RV function after restoration of pulmonary valve competency and resection of the dilated RV outflow has been demonstrated. Whether this results in improved long-term survival has not yet been established.[18] Recent data suggest that patients with intermediate RV dilatation (132 ± 9 ml/m^2) and severe PR (40 ± 3%) are at low risk of significant progression of RV size in the short term, suggesting that some delay in PVR may be acceptable in this group.[23] PVR may also induce some degree of RVOT stenosis, as was noted in our patient group. This could be caused by the use of a relatively small homograft or by deterioration of the homograft.[24]

The lack of change in important pro-arrhythmic parameters, such as QRS duration and QTc time, reflects earlier observations.[18] In a study that has been criticized for problems related to adequate matching of the groups involved, Harrild et al.[18] could not demonstrate a beneficial effect of PVR with regard to post-PVR occurrence of ventricular tachycardia or death. The implications of these observations are that current long-term treatment strategies may require modification.[17]

A common indication for reintervention after ToF repair is prevention or treatment of haemodynamically important arrhythmias. The burden of arrhythmias is considerable in these patients, particularly in the adult age range. Atrial arrhythmias occur frequently, in up to one-third of the patients.[20] Pacemaker implantation, for bradycardia and tachycardia/bradycardia syndromes, is required in up to 8%.[20] Haemodynamic factors and prior surgeries are among the most important risk factors. In our population, pacemaker implantation was relatively infrequent and was required only in the TP group.

More than moderate TR may be another indication for reintervention. The occurrence of more than minimal TR in our series was limited and comparable/compares favourably with other recent reports. Important TR may relate to intrinsic valve abnormalities, traction on the tricuspid annulus or damage to tricuspid structures

during repair or to RV dilatation in the setting of impaired RV function.[19] In recent series, late TR did not differ between transatrial and transventricular approaches to ToF repair.

Since the 1970s, less than 10% of ToF repairs in our institutions have been performed with the transventricular approach, which has hampered a direct comparison between results of transatrial and transventricular repairs. Recent single- and multicentre data suggest that both techniques can be used successfully. Ventriculotomy has been thought to contribute to long-term impairment of right ventricular function and the risk of ventricular arrhythmias. Whether the transatrial–transpulmonary approach has actually resulted in long-term benefits for the patients is still a subject of debate. The transatrial–tranpulmonary approach does not use a ventriculotomy in the body of the RV and a limited, if any, incision of the RV outflow tract. Comparison of results is often difficult, since different approaches in time, different anatomical variants and different age groups have been included in different studies. Furthermore, the long-term effects of the approach to VSD closure and of RV outflow desobstruction are hard to distinguish. Lindberg et al.[5] in a single-centre study of 570 patients did not find any difference in long-term outcomes of transatrial versus transventricular repair. Any transannular incision increased the risk of reinteventions, but did not impact on long-time survival.[5, 11] In the series of Alexiou et al.[14] a significantly higher reintervention rate at 10- and 20-year follow-up was noted in the atrial versus the transventricular approach, particularly for RV outflow obstruction, for reasons that were not clear to the authors. This has not been a common observation.[5, 6] Data from the Society of Thoracic Surgeons Database and of the European Association for Cardio-Thoracic Surgery Congenital Database have shown that both approaches continue to be used widely, with excellent early results and ventriculotomy and TP as the most prevalent type of operation.[3, 4] A temporal trend towards the transatrial approach has been reported in the most recent studies.[3, 21]

Study limitations

A limitation of this study is the retrospective design, resulting in a considerable number of missing values. Another limitation was the small number of patients with an event. Furthermore, a direct comparison of different surgical approaches could not be made.

Conclusions

ToF patients corrected with the transatrial–transpulmonary approach have good long-term survival. Clinical condition after ToF repair is good; PVR is a frequent event at longer follow-up, other events are limited in number. The use of a TP at ToF repair is a predictor for poorer event-free outcome; it almost doubles the risk of the composite endpoint of death, reoperation, balloon dilatation, pacemaker placement or PVR.

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Chapter 8

Long-term follow-up after transatrial-transpulmonary repair of Tetralogy of Fallot: Influence of timing on outcome

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Abstract

Objectives

Our goal was to report the long-term serial follow-up after transatrial–transpulmonary repair of (TOF) and to describe the influence of the timing of the repair on outcome.

Methods

We included all patients with TOF who had undergone transatrial-transpulmonary repair between 1970 and 2012. Records were reviewed for patient demographics, operative details and events during the follow-up period (death, pulmonary valve replacement, cardiac reinterventions and hospitalization/intervention for arrhythmias). In patients with elective early primary repair of TOF after 1990, a subanalysis of the optimal timing of TOF repair was performed.

Results

A total of 453 patients were included (63% male patients; 65% had transannular patch); 261 patients underwent primary elective repair after 1990. The median age at TOF repair was 0.7 years (25th-75th percentile 0.3–1.3) and decreased from 1.7 to 0.4 years from before 1990 to after 2000, respectively ($p<0.001$). The median follow-up duration after TOF repair was 16.8 years (9.6–24.7). Events developed in 182 (40%) patients. In multivariable analysis, early repair of TOF (<6 months) (hazard ratio [HR] 3.06; $p<0.001$) and complications after TOF repair (HR 2.18; $p=0.006$) were found to be predictive for an event.

In a subanalysis of the primary repair of TOF after 1990, the patients (n= 125) with elective early repair (<6 months) experienced significantly worse event-free survival compared to patients who had elective repair later (n=136). In multivariable analysis, early repair (HR 3.00; $p=0.001$) and postoperative complications (HR 2.12; $p=0.010$) were associated with events in electively repaired patients with TOF.

Conclusions

Transatrial-transpulmonary repair of TOF before the age of 6 months may be associated with more events during the long-term follow-up period.

Introduction

Since the first repair of Tetralogy of Fallot (TOF) in 1954, the surgical approach and the timing of the operation have changed. Initially, a right ventricular (RV) incision with a patch across the RV outflow tract (RVOT) was performed. In the current era, the primary transatrial-transpulmonary approach with the intention to minimize the use of a transannular patch (TP) is commonly used.[1-3] The goal of this transatrial-transpulmonary approach is to preserve the integrity of the pulmonary annulus and to avoid a ventriculotomy. This approach potentially reduces myocardial scarring and ventricular dilatation.[1, 2] These changes in surgical techniques together with improvements in cardiopulmonary bypass techniques and perioperative management have been associated with increased survival rates.[1, 2]

The age at which TOF is repaired has decreased over time.[2-5] However, there is no consensus regarding the optimal timing of the primary repair of TOF.[2, 4, 6, 7] Early primary repair of TOF is advocated by some because it minimizes the time at risk for cyanotic spells, hypoxia and RV pressure overload.[6, 8] The potential disadvantages of early repair of TOF are a longer stay in the intensive care unit, increased risk of reinterventions and more frequent use of a TP.[7, 9-12]

We previously published results of a relatively large TOF cohort operated on by the transatrial-transpulmonary approach.[2]

Considering the ongoing discussion on the timing of primary repair of TOF [2, 13], the current updated serial analysis of this identical cohort had 2 objectives: first, to investigate the current freedom from events and second, to investigate the potential influence of the timing of primary TOF repair on long-term outcomes.

Methods

Patients

All included patients had undergone transatrial-transpulmonary repair of TOF before June 2012 and were born after January 1, 1970.[2] We excluded patients with pulmonary atresia, absent pulmonary valve syndrome, double outlet RV and atrioventricular septal defect, with missing surgical reports or in whom a primarily trans-ventricular approach was used. The local ethics committees approved this retrospective study and waived informed consent.

Events

The medical records of all patients were reviewed through December 2017. Cardiac events during the follow-up period were recorded until the patient's latest visit to the outpatient clinic. All patients were followed according to regular follow-up protocols. The latest information for these follow-up visits was obtained for >85% of patients within 4 years before data acquisition. For mortality rate analysis, each patient's status

was checked in municipal administrative records. Early complications after TOF repair were defined as complications within 30 days or during the hospital stay.[14] After TOF repair, the following early postoperative complications were recorded: infection, arrhythmia, chylothorax, post-pericardiotomy syndrome, fluid retention, prolonged use of inotropic drugs (>48 h), early reoperation and early death. Long-term events were defined as all-cause mortality, pulmonary valve replacement (PVR), cardiac reoperations, catheter-based reinterventions and arrhythmias that required intervention and/or hospitalization. Patients lost to follow-up were censored at the last known follow-up date.

Elective repair of Tetralogy of Fallot

A subgroup analysis was performed regarding the optimal timing of primary TOF repair in electively repaired patients. TOF repair before the age of 6 months was considered early; repair when the patient was older than 6 months was considered late. For this analysis, patients with a palliative shunt, a duct-dependent circulation and a balloon pulmonary valvuloplasty or RV outflow stent prior to TOF repair were excluded. Also, patients who had a non-elective operation, defined as a TOF repair within 72 h of worsening cyanosis or cyanotic spells, were excluded.

Prior to the year 2000, the 2 centres in this study had the same surgical practice regarding the timing of TOF repair, and the age at TOF repair did not differ between the centres. After the year 2000, one of the centres opted for earlier primary TOF repair around the age of 3 months. This practice resulted in a difference in median age at TOF repair in the cohort after 2000. In the Netherlands, referral to a specific centre is based mainly on where the patient lives.

Statistical analyses

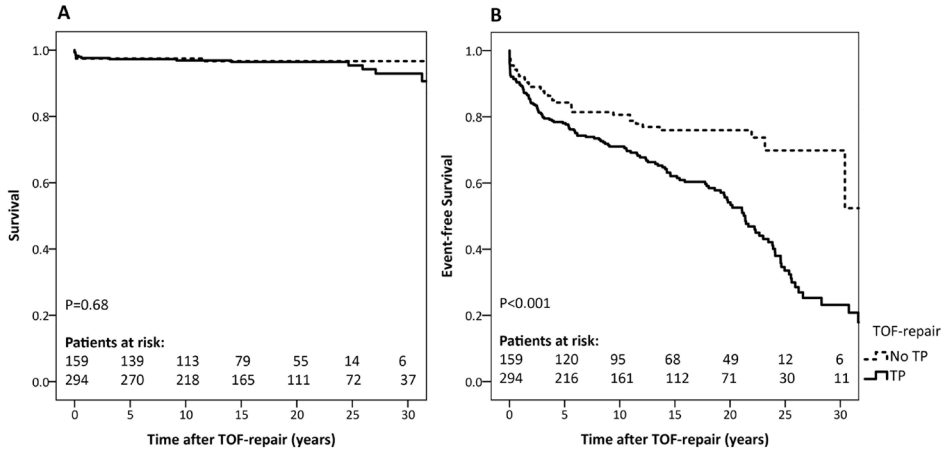
Continuous variables with a normal distribution were summarized as the mean (standard deviation). Variables with a non-normal distribution were presented as the median (25^{th}-75^{th} percentiles). Differences between groups were analysed using the Student *t*-test or the Mann-Whitney U-test. Categorical variables were presented as numbers and percentages and were evaluated by the χ^2 test.

The incidence of the events over time was evaluated according to the Kaplan-Meier method; differences between groups were evaluated using the log-rank test. The Cox proportional hazard analysis was used to determine whether factors had an influence on the probability of the event. We found no deviations of the proportional hazards assumption by inspecting the plots of log minus log survival functions. Potential factors associated with events—selected from the literature—were explored in univariable Cox regression models. All factors from the univariable analyses were included in the multivariable backward model in which a p-value of <0.157 was required for the factor to be retained in the model. All analyses were performed using SPSS version 25.0 (IBM Corp. Armonk, NY USA). Two-sided p-values <0.05 were considered statistically significant.

Results

We included 453 patients. The median age at TOF repair was 0.7 (0.3–1.3) years.[2] A TP was used in 294 (65%) patients (Table 1). The total analysis comprised 7505 patient-years (5118 TP; 2387 non-TP). The maximum follow-up after TOF repair was 40.6 years, with a median follow-up of 16.2 (9.2–22.8) years.

Figure 1. (A) Overall survival; **(B)** event-free survival after TOF repair.



Abbreviations; TOF: Tetralogy of Fallot; TP: transannular patch.

Mortality rate

The overall mortality rate was 4% (14 TP; 5 non-TP); the early mortality rate was 2%; late deaths occurred in 10 patients. For the entire cohort, the overall survival rate was 97% at 10 years (standard error [SE] 1%); 96% at 20 years [SE 1%]; 95% at 25 years [SE 1%] and 93% at 30 years [SE 2%], with no significant differences in survival between patients who had a TP and those who did not (Figure 1).

Eleven patients died of cardiac causes; 6 patients, of non-cardiac causes; and in 2 patients, the cause of death was unknown. Since our previous analysis, 3 patients died, 1 of cardiac cause.[2]

Events during the follow-up period

After TOF repair, 270 events developed in 182 (40%) patients; 55 (12%) patients developed 2 or more events. The event-free survival rate was 74% at 10 years (SE 2%), 62% at 20 years (SE 3%) and 34% at 30 years (SE 4%). Non-TP patients experienced a better event-free survival rate ($p<0.001$) (Figure 1). However, events developed earlier in the non-TP group at a median of 2.9 (0.5–7.6) versus 6.9 (2.1–19.9) years after TOF repair ($p=0.02$) (Table 1).

Table 1. Patient, surgical and outcome characteristics

	All patients (n=453)	TP (n=294)	Non-TP (n=159)	P-value
Patient and surgical characteristics				
Male (n, %)	286 (63.1)	183 (62.0)	103 (65.2)	0.51
Birth weight (kg)	3.0 (2.5–3.6) (n=267)	3.1 (2.6–3.6) (n=168)	2.9 (2.4–3.5) (n=99)	0.12
22q11 deletion (n,%)	27 (6.0)	19 (6.5)	8 (4.4)	0.54
Trisomy 21 (n,%)	28 (6.2)	16 (5.4)	12 (7.6)	0.38
Previous balloon dilatation (n,%)	6 (1.3)	5 (1.7)	1 (0.6)	0.67
Previous palliative shunt (n,%)	55 (9.5)	43 (18.0)	12 (7.5)	0.03
Age of TOF repair (years)	0.7 (0.3–1.3)	0.7 (0.3–1.3)	0.7 (0.4–1.4)	0.15
RVOT gradient before TOF repair (m/s)	4.4 (3.9–4.8) (n=285)	4.5 (4.0–5.0) (n=165)	4.0 (3.1–4.7) (n=118)	<0.001
Oxygen saturation at TOF repair (%)	90 (82–97) (n=214)	88 (80–95) (n=162)	96 (90–99) (n=52)	<0.001
Weight at TOF repair (kg)	7.1 (5.3–9.3) (n=442)	7.1 (5.3–8.9) (n=292)	7.3 (5.3–9.5) (n=150)	0.42
Aortic cross-clamp time (min)	77 (57–107) (n=298)	74 (57–105) (n=188)	83 (59–114) (n=110)	0.34
Valvulotomy (n,%)	176 (3.9)	79 (26.8)	97 (61.4)	<0.001
ICU stay (days)	3.0 (2.0–4.0) (n=408)	3.0 (2.0–4.0) (n=270)	2.0 (2.0–3.0) (n=138)	<0.001
Postoperative complications (n,%)	102 (22.5)	78 (26.5)	24 (15.1)	0.007
Early reoperation (n,%)	20 (4.4)	18 (6.1)	2 (1.3)	0.01
Early death (n,%)	9 (2.0)	5 (1.7)	4 (2.5)	0.14
Outcomes during follow-up				
Age at end of follow-up (years)	17.4 (10.6–24.8)	17.6 (10.6–26.1)	15.8 (10.6–23.1)	0.063
Time after TOF repair (years)	16.8 (9.5–23.1)	17.3 (10.0–25.0)	15.3 (9.0–22.0)	0.030

Patients with events (n,%)	182 (40.2)	145 (49.3)	37 (23.3)	<0.001
Time after TOF repair (years)	5.4 (1.2–17.8)	6.9 (2.1–19.6)	2.9 (0.5–7.6)	0.02
Deceased (n,%)	19 (4.2)	14 (4.8)	5 (3.1)	0.41
PVR (n, %)	88 (19.4)	86 (29.3)	2 (1.3)	<0.001
Time after TOF repair (years)	19.6 (12.7–23.7)	19.6 (12.6–23.9)	18.2	0.98
Second PVR (n, %)	10 (2.2)	10 (3.4)	0 (0)	0.02
Other late reoperations (n,%)	58 (12.8)	36 (12.2)	22 (13.8)	0.66
Time after TOF repair (years)	2.6 (1.3–5.7)	2.2 (1.2–5.5)	3.5 (1.3–6.0)	0.46
HC intervention for PS (n,%)	38 (8.4)	30 (10.2)	8 (5.0)	0.06
Pacemaker (n,%)	5 (1.1)	5 (1.7)	0 (0)	0.17
ICD (n,%)	1 (0.2)	1 (0.3)	0 (0)	1.00

Results are given as mean (standard deviation), as median (25th-75th percentile) or as counts (percentages).
Abbreviations; HC: heart catheterization; ICD: implantable cardioverter defibrillator; ICU: intensive care unit; PVR: pulmonary valve replacement; PS: pulmonary stenosis; RVOT: right ventricular outflow tract; TOF: Tetralogy of Fallot; TP: transannular patch.

A total of 88 (19%) patients received a PVR: 29% in the TP group versus 1% in the non-TP group (p<0.001). The PVR-free survival rate was 96% at 10 years (SE 1%), 83% at 20 years (SE 2%) and 48% at 30 years (SE 5%) after TOF repair. Since our previous analysis, 36 patients received a first PVR.

Excluding PVR, other late reoperations were performed in 58 (13%) patients, 6 more since the previous analysis. The main indication for late reoperations was residual RVOT obstruction and trunk or branch pulmonary stenosis (PS) in 47 patients. Other reoperations were for a ventricular septal defect (n= 4), a ventricular septal defect and RVOT obstruction or PS (n= 5) and other causes (n= 2).

A total of 23 percutaneous interventions for valvular PS and 33 for branch PS were performed in 38 (8%) patients. Eighteen (4%) patients needed percutaneous interventions for valvular PS; 18, for branch PS (4%); and 2 patients needed both. In 3 patients a stent was implanted in the RVOT prior to PVR and an aorta-pulmonary collateral was closed in 1 patient.

Late after TOF repair, 5 patients received a pacemaker and 1 patient, an implantable cardioverter defibrillator due to heart failure. Two patients needed a catheter ablation for ventricular arrhythmias; 2 patients needed a catheter ablation for atrial flutter; and 1 patient needed an ablation for Wolf-Parkinson-White syndrome. One patient was hospitalized due to a self-limiting arrhythmia.

Early versus late primary repair of Tetralogy of Fallot

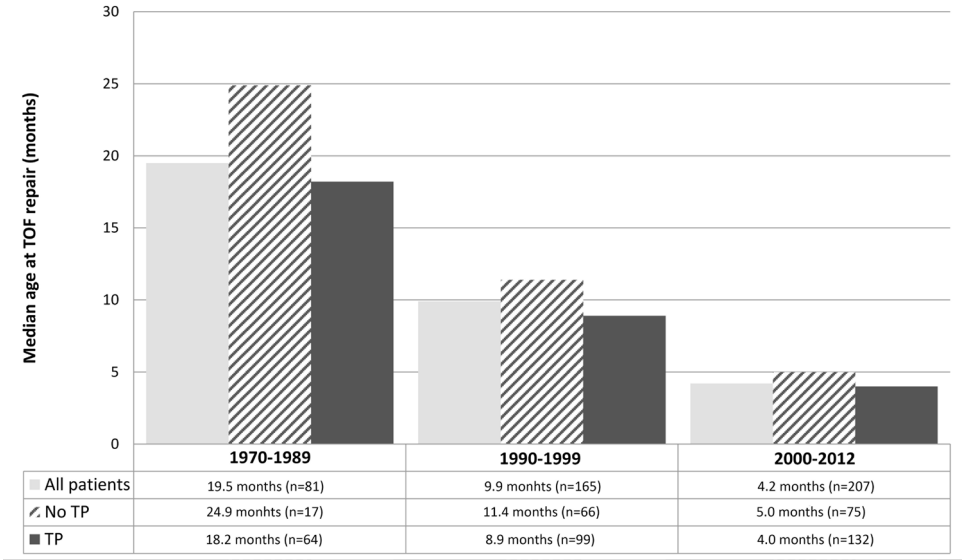
Figure 2 and Table 2 show the decrease in age at TOF repair. Before 1990, the median age at TOF repair was 19.5 (9.1–48.4) months compared to 6.5 (3.5–11.5) months after 1990 (p<0.001). Likewise, patients in the 1990-1999 cohort were significantly older at TOF repair compared to those in the 2000-2012 cohort: 9.9 (5.3–15.7) versus 4.2 (3.0–10.1) months (p<0.001). Patients in the youngest cohort at TOF repair (2000-2012) experienced the worst event-free survival rate (Figure 3). There is a strong, significant correlation between weight and age at TOF repair (r=0.924; p<0.001).

To explore the potential influence of timing of TOF repair on outcomes, we performed a subanalysis of patients who underwent primary elective TOF repair after 1990 (n=261). The patient characteristics and outcomes of the primary elective TOF repair group are shown in Table 3. A TP occurred significantly more often in the early repair group compared to the late repair group: 64.0% versus 51.5% (p=0.046).

Prior to TOF repair, no differences in oxygen saturation were observed between the total early repair and late repair groups. The median echocardiographic RVOT velocity, indicating the gradient, was slightly higher in the early repair group compared to the late repair group: 4.6 (4.0–5.0) versus 4.3 (4.0–4.7) m/s (p=0.047). A shorter interval between the echocardiogram before surgery and the TOF repair was observed in the early repair group compared to the late repair group: 33 (17–48) versus 67 (35–110) days (p<0.001).

Despite a significantly shorter median follow-up period in the early repair group, significantly more events developed in the early repair group (37% vs 20%; p=0.003). A total of 30 patients received a PVR: 8.8% in the early repair group versus 13.9% in the late repair group (p=0.24). The overall PVR-free survival rate in the primary elective

Figure 2. Median age at TOF repair over time.



Abbreviations; TOF: Tetralogy of Fallot; TP: transannular patch.

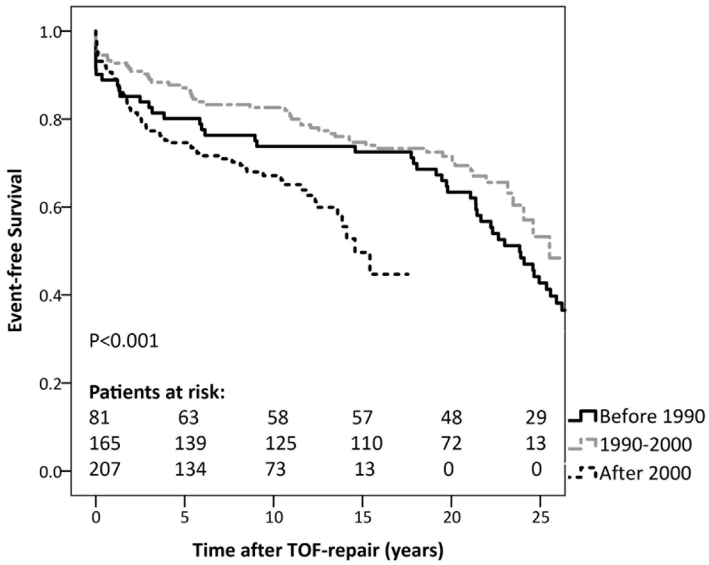
Table 2. Characteristics of repair of Tetralogy of Fallot over time

	TOF repair before 1990[1]	TOF repair 1990-2000[2]	TOF repair >2000[3]	P-value[1-2*]	P-value[2-3*]
Number of patients (n, %)	81 (17.9)	165 (36.4)	207 (45.7)		
Median age at TOF repair (months)	19.5 (9.1–48.4)	9.9 (5.3–15.7)	4.2 (3.0–10.1)	<0.001	<0.001
Previous balloon dilatation (n, %)	0 (0.0)	1 (0.6)	5 (2.4)	1.00	0.23
Previous palliative shunt (n, %)	9 (11.1)	23 (13.9)	24 (11.6)	0.54	0.50
Transannular patch (n, %)	64 (79.0)	98 (59.4)	132 (63.8)	0.002	0.39
Early reoperation (n, %)	9 (11.1)	6 (3.6)	5 (2.4)	0.021	0.55
Early death (n, %)	2 (1.2)	2 (2.5)	5 (2.4)	0.600	0.47

*A p-value of <0.025 can be considered statistically significant after the Bonferroni correction.
Results are given as mean (standard deviation), as median (25th-75th percentile) or as counts (percentages).
Abbreviation; TOF: Tetralogy of Fallot.

TOF repair group was 97% at 10 years (SE 1%), 85% at 20 years (SE 3%) and 66% at 25 years (SE 6%). The reported difference in events was mainly driven by late reoperations other than PVR (n=27), 22 (17.6%) in the early repair group versus 5 (3.7%) in the late repair group (p<0.001). The main reason for late reoperation other than PVR was residual RVOT obstruction and trunk or branch PS in 24 patients. In 1 patient, a residual VSD was closed and the trunk PS was relieved; in 1 patient a VSD was closed and in 1 patient the patent ductus arteriosus was closed. Figure 4 shows that patients in the late repair group had a significantly better event-free survival rate (p<0.001).

Figure 3. Event-free survival for the different surgical decades.



Abbreviation; TOF: Tetralogy of Fallot.

Predictors for events

In Table 4, the Cox proportional hazard analysis is shown for all patients (n= 453). In univariable analysis, TP, postoperative complications, early TOF repair and year of TOF repair were found to be predictive for events. Multivariable analysis showed that patients were significantly more likely to experience an event if they had an early TOF repair (HR 3.06, CI 1.67–5.61) or a postoperative complication (HR 2.18, 95% CI 1.25–3.83).

Table 4 shows the Cox proportional hazard analysis for the patients who underwent primary elective TOF repair after 1990 (n=261). Multivariable analysis showed that patients were significantly more likely to experience an event if they had an early TOF repair (HR 3.06, 95% CI 1.67–5.61) or postoperative complications (HR 2.18, 95% CI 1.25–3.83).

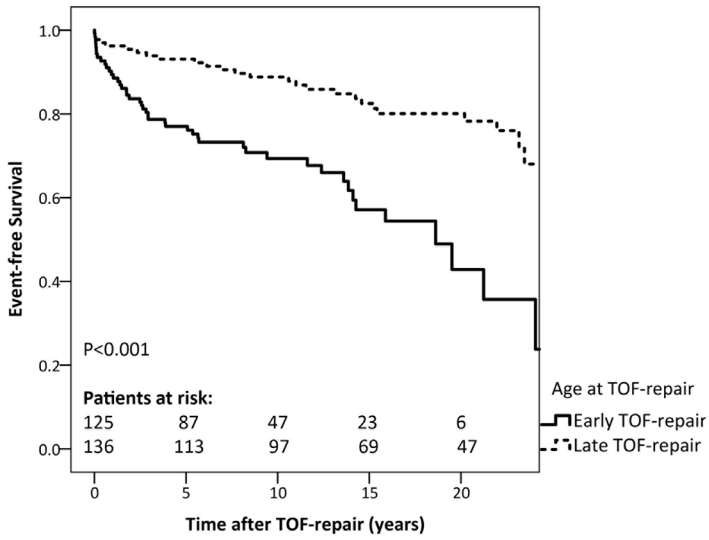
In the primary elective repair group, female patients experienced a worse event-free survival rate (p=0.010). No gender differences were observed in the median age at TOF repair, degree of RVOT obstruction (RVOTO) before TOF repair or the use of a TP. There was also no significant difference in weight at TOF repair in male versus female patients. In the overall patient group, no difference in the event-free survival rate between gender was observed.

Table 3. Patient, surgical and outcome characteristics for primary elective repair of Tetralogy of Fallot after 1990.

	Early TOF repair (n=125)	Late TOF repair (n=136)	P-value
Patient and surgical characteristics			
TOF repair after 2000 (n,%)	94 (75.2)	54 (39.7)	<0.001
Male (n, %)	76 (60.8)	90 (66.2)	0.37
Birth weight (kg)	3.2 (2.6–3.7) (n=80)	2.9 (2.5–3.5) (n=67)	0.094
22q11 deletion (n,%)	14 (11.2)	8 (5.9)	0.18
Trisomy 21 (n,%)	4 (3.2)	11 (8.1)	0.075
Age TOF repair (years)	0.29 (0.23–0.39)	0.95 (0.68–1.43)	<0.001
RVOT gradient before TOF repair (m/s)	4.6 (4.0–5.0) (n=116)	4.3 (4.0–4.7) (n=105)	0.047
Time between repair and presurgical echocardiogram (days)	33 (17–48) (n=16)	67 (35–110) (n=105)	<0.001
Oxygen saturation at TOF repair (%)	95 (85–99) (n=73)	91 (85–98) (n=54)	0.80
Weight at TOF repair (kg)	5.3 (4.6–6.2) (n=121)	8.6 (7.4–9.6) (n=133)	<0.001
Aortic cross-clamp time (min)	66 (47–90) (n=65)	90 (61–115) (n=109)	<0.001
TP (n,%)	80 (64.0)	70 (51.5)	0.046
Valvulotomy (n,%)	33 (26.4)	70 (51.5)	<0.001
ICU stay (days)	3.0 (2.0–4.0) (n=20)	3.0 (2.0–3.0) (n=117)	0.85
Postoperative complications (n,%)	28 (22.4)	19 (14.0)	0.11
Early reoperation (n,%)	4 (3.2)	2 (1.5)	0.30
Early death (n,%)	4 (3.2)	1 (0.7)	1.00
Gradient RVOT after TOF repair (m/s)	2.7 (2.0–3.3) (n=99)	2.5 (2.2–3.2) (n=99)	0.71
Time between TOF repair and post-surgical echocardiogram (days)	7 (6–8) (n=99)	7 (6.5–9) (n=99)	0.058
Outcomes during follow-up			
Age at end of follow-up (years)	12.5 (7.1–17.2)	18.8 (11.8–23.8)	<0.001
Time after TOF repair (years)	12.1 (6.8–16.8)	18.0 (10.6–22.4)	<0.001
Patients with events (n,%)	46 (36.8)	28 (20.6)	0.004
Time after TOF repair (years)	2.7 (0.8–10.0)	9.6 (2.5–16.0)	0.022
Deaths (n,%)	5 (4.0)	1 (0.7)	0.107
PVR (n,%)	11 (8.8)	19 (13.9)	0.24
Time after TOF repair (years)	15.8 (12.4–19.5)	14.6 (7.7–22.0)	0.97
Other late reoperations (n,%)	22 (17.6)	5 (3.7)	<0.001
Time after TOF repair (years)	2.8 (1.3–7.1)	3.1 (1.2–5.8)	0.98
HC intervention for PS (n,%)	12 (9.6)	7 (5.1)	0.23
Pacemaker (n,%)	1 (0.8)	0	0.48
ICD (n,%)	0 (0)	0 (0)	-

Results are given as mean (standard deviation), as median (25th-75th percentile) or as counts (percentages). Abbreviations; TOF: Tetralogy of Fallot; RVOT: right ventricular outflow tract; TP: transannular patch; ICU: intensive care unit; PVR: pulmonary valve replacement; HC: heart catheterization; PS: pulmonary stenosis, ICD: implantable cardioverter defibrillator.

Figure 4. Event-free survival for early versus late primary elective TOF repair after 1990.



Abbreviation; TOF: Tetralogy of Fallot.

Discussion

This study is one of the largest describing several decades of serial follow-up in transatrial-transpulmonary repair in patients with TOF. Our main findings are that survival is good, but long-term morbidity may increase in patients who have an early repair. Furthermore, long-term morbidity after transatrial-transpulmonary TOF repair remains high. Compared to our previous analysis of the same cohort (2015), longitudinal follow-up showed an increase of 0.7% (n=3) in the mortality rate and 7.9% (n=36) of PVR over a 3.5-year period.

Timing of repair of Tetralogy of Fallot

The debate regarding the optimal timing of primary TOF repair is ongoing, and the data on this topic with sufficient follow-up duration are relatively scarce.[4, 6, 7, 15]

Our study stands out because of the relatively long follow-up period.[12, 16-18] In agreement with much of the literature, we observed a significant decrease in the median age at TOF repair over time.[2-5] Remarkably, patients in our 2000-2012 cohort with the lowest age at TOF repair (4.2 months) experienced the worst event-free survival.

We analysed the whole group (n= 453) and the electively repaired patients after 1990 (n= 261) separately. For this analysis we excluded patients with previous palliation or

Table 4. Predictors for the composite end point for all patients and for patients with an elective primary Tetralogy of Fallot repair after 1990

	Univariable			Multivariable		
	Hazard ratio	**95% CI**	**P-value**	**Hazard ratio**	**95% CI**	**p-value**
All patients (n=453)						
Female	1.22	0.90 to 1.64	0.20	-		
Centre	1.27	0.91 to 1.79	0.16	-		
22q11 deletion	0.82	0.40 to 1.67	0.59	-		
Year of TOF repair	1.02	1.00 to 1.05	0.026	-		
TOF repair <6 months	1.87	1.37 to 2.54	<0.001	3.06	1.67 to 5.61	<0.001
RVOT obstruction at TOF repair (m/s)	1.31	0.98 to 1.73	0.065	-		
TP	2.18	1.52 to 3.13	<0.001	-		
Complications after TOF repair	3.03	2.21 to 4.15	0.017	2.18	1.25 to 3.83	0.006
Elective primary repair patients (n=261)						
Female	1.81	1.15 to 2.87	0.011	-		
Centre	1.55	0.94 to 2.56	0.086	-		
22q11 deletion	1.39	0.66 to 2.89	0.39	-		
Year of TOF repair	1.08	1.03 to 1.13	0.001	-		
TOF repair <6 months	2.85	1.76 to 4.64	<0.001	3.00	1.61 to 5.60	0.001
RVOT obstruction at TOF repair (m/s)	1.26	0.90 to 1.76	0.19	-		
TP	1.86	1.12 to 3.10	0.017	-		
Complications after TOF repair	3.30	2.01 to 5.40	<0.001	2.12	1.20 to 3.78	0.010

Results are given as mean (standard deviation), as median (25th-75th percentile) or as counts (percentages). Abbreviations; CI: confidence interval; RVOT: right ventricular outflow tract; TOF: Tetralogy of Fallot; TP: transannular patch.

with nonelective surgery, because they probably reflect the more severe spectrum of TOF. In the subanalyses of elective primary TOF repair, patients with early repair received more TPs and experienced significantly worse event-free survival rates compared to patients with late primary TOF repair. We assessed relevant preoperative clinical parameters that might have affected this outcome. The degree of RVOTO was slightly higher in the early repair group. This result might indicate a somewhat more severe phenotype in the early repair group. On the other hand, considering the longer time between assessment of the RVOTO and TOF repair in the late repair group, it is possible that there was a larger increase of the RVOTO after assessment in the late repair group. Postoperative data indicated similar relief of RVOTO in both groups (RVOT velocities 2.7 [2.0–3.3] vs 2.5 [2.2–3.2] m/s; p=0.71). However, during follow-up, late reoperations, usually for residual RVOTO, were significantly more prevalent in the early repair group. Cunningham[18] also observed that, despite similar residual RVOTO of <20

mm Hg after TOF repair, reinterventions were more common when the TOF repair was performed before 55 days of age. Possibly there is a difference in growth of the (branch) pulmonary arter(y)(ies) between patients operated on early or later in life[18] or a patient-size difference in the size of the TP, resulting in more PR/PS and the subsequent need for reinterventions.

Some researchers observed that repair before the age of 28 days is associated with more TPs, longer hospital stay and increased mortality rate.[7, 17, 19, 20] Studies in patients beyond the neonatal age found that an older age at complete TOF repair is associated with shorter hospital stays and lower mortality rates.[16, 17, 20-22] Dorobantu [16] observed, in a large (n=1662) study with a median follow-up of 4.7 years, that at 12 years the mortality rate was higher when repair was performed before the age of 60 days. However, these studies often have limited follow-up duration. In our electively repaired cohort, the median follow-up after TOF repair was 13.9 years.

It is hard to determine whether our findings relate to more severe anatomical defects and therefore the need for the earlier TOF repair. However, the combined findings from the literature may indicate that it might be better to postpone primary elective TOF repair in asymptomatic patients with TOF until at least 6 months of age. Recently, interest has increased in transcatheter RVOT palliation prior to primary repair, potentially postponing repair in symptomatic patients with TOF.[16, 17, 20]

Survival

Recent observations point towards increased survival after TOF repair performed in past decades, which is mainly driven by the decrease in early mortality rates.[2, 5, 11, 23] We observed an overall survival rate of 96% at 20 years and of 93% at 30 years. Relatively few studies have reported the 25- to 30-year survival rates of contemporary surgical approaches. D'Udekem.[11] described a 97% 25-year survival rate in a large cohort operated on after 1980, with only 16 patients followed up 25 years after TOF repair. Park [5] described, in a cohort operated on after 1986, a 25-year survival rate of 93%. In our study, the overall survival rate was higher, which may relate in part to differences in the composition of the diagnoses of the populations.[5]

Morbidity

Morbidity remains high after TOF repair, with worse survival in patients who have a TP. The use of a TP damages the integrity of the pulmonary valve and the RVOT, causing PR.[13, 23] Long-term exposure to moderate to severe pulmonary regurgitation (PR) causes RV dilatation, impaired ventricular function and arrhythmias that often require reinterventions.[1, 13, 23] Over time, attempts were made by surgeons to avoid or minimize the use of a TP, and new valve-sparing techniques were developed.[3] In patients with narrow RVOTs, a TP might be necessary and cannot be avoided, but TP use also differs among surgeons.[24]

Gender

In patients who had elective primary repair after 1990, we observed a significantly better event-free survival in male compared to female patients. The reason for this is not entirely clear. We did not observe this difference in the overall cohort. Gender differences in PS or valve sizes have not been reported. In older patients with TOF, male gender was associated with ventricular tachyarrhythmias, a larger cardiac mass, biventricular volumes and peak VO_2, but a lower ejection fraction.[25, 26] These factors may affect long-term morbidity and survival rates.[13]

Study limitations

Due to the retrospective nature of this study, we had missing values. Our study represents the experience of 2 centres. After the year 2000 there was a difference in age of TOF repair between the 2 centres, which could have influenced our results. We also did not perform a competing risk analysis.

Likewise our study shows the experience after TOF repair over multiple decades. During this time, the availability of diagnostic methods, indications for and timing of (re) interventions has changed, which could have influenced our results and could therefore be a bias.

Conclusions

The transatrial-transpulmonary repair of TOF before the age of 6 months is associated with more events during long-term follow-up, mainly due to an increase in interventions for RVOT obstruction. We noted a trend towards a decrease of age at TOF repair. These findings suggest that, if clinically feasible, it may be better to delay primary TOF repair as long as possible. Further prospective studies are needed to determine the optimal timing for primary repair of TOF.

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Chapter 9

Ventricular response to dobutamine stress cardiac magnetic resonance imaging is associated with adverse outcome during 8 year follow-up in patients with repaired Tetralogy of Fallot

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Abstract

Aims

The aim of this study was to evaluate the possible value of dobutamine stress cardiac magnetic resonance imaging (CMR) to predict adverse outcome in Tetralogy of Fallot (TOF) patients.

Methods and results

In previous prospective multicentre studies, TOF patients underwent low-dose dobutamine stress CMR (7.5 µg/kg/min). Subsequently, during regular-care patient follow-up, patients were assessed for reaching the composite endpoint (cardiac death, arrhythmia-related hospitalization or cardioversion/ablation, VO_2 max ≤65% of predicted). A normal stress response was defined as a decrease in end- systolic volume (ESV) and increase in ejection fraction. The relative parameter change during stress was calculated as relative parameter change= [(parameter$_{stress}$− parameter$_{rest}$)/ parameter$_{rest}$] *100. The predictive value of dobutamine stress CMR for the composite endpoint was determined using time time-to-event analyses (Kaplan-Meier) and Cox proportional hazard analysis.

We studied 100 patients (67 (67%) male, median age at baseline CMR 17.8 years (IQR 13.5–34.0), age at TOF repair 0.9 years (0.6–2.1)). After a median follow-up of 8.6 years (6.7–14.1), 10 patients reached the composite endpoint. An abnormal stress response (30% vs 4.4%, p=0.021) was more frequently observed in composite endpoint patients. Also in endpoint patients, the relative decrease in right ventricular ESV decreased less during stress compared to the patients without an endpoint (-17±15 vs -26±13 %, p=0.045). Multivariable analyses identified an abnormal stress response (HR 10.4; 95% CI 2.5–43.7; p=0.001) as predictor for the composite endpoint.

Conclusions

An abnormal ventricular response to dobutamine stress is associated with adverse outcome in patients with repaired TOF.

Introduction

Survival after surgical repair of Tetralogy of Fallot (TOF) in infancy is good, long-term survival of 95% at 10-year and >90% at 25 year has been reported.[1-3] However, TOF patients frequently develop long-term problems such as pulmonary regurgitation (PR), right ventricular (RV) dilatation, ventricular dysfunction, arrhythmias and even mortality.[1, 2, 4, 5]

In TOF patients, peak VO_2, NT-proBNP levels and QRS duration have been related to ventricular volumes, function and outcome.[6-10] RV end diastolic volume (EDV), LV end systolic volume (ESV), LV ejection fraction (EF) and myocardial deformation parameters are associated with sudden cardiac death, severe arrhythmias and heart failure.[8, 11-13] Nonetheless, additional parameters are needed for better risk stratification.[5] This search for additional outcome determinants is hampered by long symptom-free intervals and therefore surrogate outcome markers are often used.[14]

A potential additional parameter is a dobutamine stress CMR. This technique combines the gold standard for volumetric cardiac parameters with functional information during (dobutamine) stress.[14] Compared with healthy volunteers, TOF patients often have an abnormal decrease in RVEDV, an impaired decrease in RVESV and an impaired increase RVEF following the use of dobutamine stress.[15-18] Luijnenburg *et al*.[17] showed that this poorer RVEF stress response is associated with a larger decrease in peak VO_2 at 5 year follow-up. Ventricular response to exercise or dobutamine stress CMR might help identifying patients at risk for developing an event.[19, 20]

Our aim was to evaluate the possible additional value of stress CMR, compared to the existing parameters, to predict adverse outcome in TOF patients.

Methods

Patients

We included TOF patients that underwent successful dobutamine stress CMR in four prospective studies in tertiary referral centers between 2002 and 2012.[17, 21-23] The institutional review boards approved the studies. All participants, and if necessary their parents, gave written informed consent before inclusion. The inclusion and exclusion criteria, study protocol, methods, adverse event rate and results have been published previously.[17, 21-23]

Patients underwent the baseline CMR study at rest and during low-dose dobutamine stress. NT-proBNP was measured with the Elecsys electrochemiluminescence immunoassay (Roche Diagnostics) and cardiopulmonary exercise testing (CPET) was performed according to previously described standardized protocols within one year from the dobutamine CMR.[17, 21-23] From that CPET the baseline peak VO_2 was assessed and expressed as percentage of predicted values. Exercise tests with a peak respiratory exchange rate of ≥1.0 were included in the analysis.

Composite study endpoint

After the study examination patients received regular patient specific care in the outpatient clinic. Since information on how to interpret stress CMR in TOF patients was not available at that time, stress CMR parameters were not used for clinical decision making.

Before data acquisition we defined our study endpoint as a composite of cardiac death, hospitalization for arrhythmias or cardioversion/ablation for arrhythmias and reaching a CPET VO_2 max below 65% of predicted (due to cardiac reasons) during follow-up after the study CPET.[9, 10] The medical records of all patients were reviewed up until January 2019.

CMR acquisition and analysis

All participants underwent CMR on the locally available scanners with dedicated phased-array cardiac surface coils. All images were obtained during breath-hold. CMR imaging was performed at rest and repeated during continuous infusion of low-dose (7.5 μg/kg/min) dobutamine hydrochloride (Centrafarm Services, Etten-Leur, the Netherlands). The dobutamine infusion was decreased (or stopped if necessary) when the heartrate increased >50%, if the systolic and/or diastolic blood pressure increased >50% or decreased >20%, if serious arrhythmias occurred, or if a patient did not tolerate the dobutamine effect. Technical details on our rest and dobutamine stress protocol have been published previously.[17, 21-23]

Analysis was performed with the software packages MASS and FLOW (Medis Medical Imaging Systems, Leiden, the Netherlands). Contours were manually drawn, under supervision of an experienced observer (WAH), in end-diastole and end-systole. Papillary muscle and large trabeculae were excluded from the blood pool. Biventricular EDV and ESV were obtained and used to calculate the EF. All ventricular volumes were indexed (i) for body surface area.

A normal stress response to low-dose dobutamine in healthy individuals consist of a decrease in ESV and a subsequent increase in EF.[15] Therefore an abnormal response to stress was defined as the inability to decrease ESV during stress and/or the inability to increase EF. Relative changes in CMR parameters were calculated as follows: relative parameter change= $[(\text{parameter}_{\text{stress}} - \text{parameter}_{\text{rest}})/\text{parameter}_{\text{rest}}] * 100$.

Statistical methods

Continuous variables with a normal distribution were summarized as mean (standard deviation (SD)). Differences between groups were analysed by Student's t-tests. Variables with a non-normal distribution were presented as median (interquartile range), and between-group differences were analysed by Mann-Whitney U tests. Categorical variables were presented as numbers and percentages, whereas between-group differences were evaluated by Chi-square tests or the Fisher's exact test. Differences between rest and stress CMR measurements were analysed with paired Student's t-tests.

The correlation between relative change in RVESV and NTproBNP was evaluated with the Spearman's rank correlation. The cumulative endpoint-free survival was estimated with Kaplan-Meier curves and differences between patients with and without the cumulative endpoint were evaluated by the log-rank test. We applied Cox proportional hazard regression analyses to relate CMR parameters, age at CMR, NTproBNP levels and QRS-duration with endpoint-free survival. In a multivariable cox regression model we included NTproBNP and a CMR stress parameter We performed two separate multivariate analyses with two parameters instead of a multivariate model with more parameters due to the limited cumulative endpoints and therefore limited statistical power. All analyses were performed using the SPSS statistical software package version 24.0 (IBM Corp. in Armonk, NY, USA), two-sided p-values <0.05 were considered statistically significant.

Results

In total, 104 patients underwent dobutamine stress CMR. Of these 104, four patients were not included in the final analysis because the dobutamine infusion had to be terminated or decreased because of adverse effects such as ventricular bigeminy and >50% increase of heartrate. These adverse effects recovered spontaneously directly after termination of the dobutamine infusion.[17, 21-23]

Dobutamine stress CMR was well tolerated and successfully completed in 100 patients, these were included in this analysis. The median age at dobutamine CMR was 17.8 (13.5–34.0) years, median time between the TOF repair and dobutamine CMR was 16.7 (12.6–33.2) years. Patients characteristics are shown in Table 1. At dobutamine CMR 15 (15%) patients had undergone a first pulmonary valve replacement (PVR) and seven (7%) patients had a residual pulmonary stenosis with a peak gradient >30 mmHg (but <60 mmHg) measured by ultrasound.

After the stress CMR the median follow-up was 8.6 (6.7–14.1) years. At the latest follow-up, 10 patients (10%) had reached the composite endpoint, median 6.2 (3.1–13.3) years after stress CMR (Table 2). All patients were alive at their latest follow-up.

Ventricular response to stress

The results of the CMR studies are shown in Table 3. For the entire group, during dobutamine stress there was a significant decrease in LVESV (33±9 vs 22±8 ml/m^2, p<0.001) and RVESV (67±26 vs 51±23 ml/m^2, p<0.001). Both LVEF (59±7 vs 72±7%, p<0.001) and RVEF (49±7 vs 61±8%, p<0.001) increased significantly during stress. In seven patients (7%) an abnormal stress response (i. e. inability to decrease ESV and/or increase EF during stress) was observed; three patients could not increase EF, two patients could not decrease ESV during stress and in two patients no change in these parameters was noted.

Table 1. Patient characteristics at dobutamine CMR

	Total (n=100)	Composite endpoint (n=10)	No composite endpoint (n=90)	P-value*
Male (n, %)	67 (67.0)	7 (70.0)	60 (66.7)	0.83
22q11 Syndrome (n, %)	3 (3.0)	1 (10.0)	2 (2.2)	0.27
Age at CMR (years)	17.8 (13.5–34.0)	15.2 (10.4–34.6)	18.2 (14.0–34.6)	0.35
Time after TOFr (years)	16.7 (12.6–33.2)	15.6 (13.2–17.5)	17.0 (12.1–33.6)	0.30
Length (cm)	166.8 ± 15.7	166.5 ± 22.4	166.9 ± 14.9	0.96
Weight (kg)	61.5 ± 18.7	61.8 ± 23.7	61.5 ± 18.2	0.97
BSA (m^2)	61.5 ± 18.7	1.7 ± 0.44	1.68 ± 0.32	0.99
Palliative shunt (n, %)	18 (18.0)	1 (10.0)	17 (18.9)	0.69
Age at TOFr (years)	0.9 (0.6–2.1)	0.6 (0.2–1.6)	1.0 (0.6–2.1)	0.076
Transannular patch (n, %)	80 (80.0)	8 (80.0)	72 (80.0)	1.00
PVR at baseline (n, %)	15 (15.0)	3 (30.0)	12 (13.3)	0.17
Pulmonary stenosis at baseline# (n, %)	7 (7.0)	1 (1.0)	6 (6.0)	0.53
QRS duration (ms)	129±24 (n=98)	134±23 (n=10)	129±25 (n=85)	0.50
NT-proBNP (µmol/l)	12.9 (6.8–21.2) (n=96)	16.4 (10.7–41.2) (n=10)	12.4 (6.6–20.3) (n=86)	0.13
Peak VO_2 (ml/min/kg)	35.7±9.5 (n=92)	35.6±9.6 (n=7)	37.6±8.2 (n=85)	0.60
Peak VO_2 (% predicted)	89.9±19.3 (n=92)	89.8±19.3 (n=7)	92.1±21.1 (n=85)	0.76

*: P-value between patients with and without a composite endpoint.
#: >30 mmHg (but <60 mmHg) measured by ultrasound
Results are given as mean (SD), as median (IQR) or as counts (percentages).
Abbreviations; TOFr: Tetralogy of Fallot repair, CMR: Cardiovascular magnetic resonance imaging, PVR: pulmonary valve replacement, VO_2: oxygen uptake.

Study endpoints

There was no difference in median age at dobutamine CMR between the patients who did and did not reach the composite endpoint. NT-proBNP levels, predicted-peak VO_2 and rest CMR parameters did not differ between both groups (Table 1, Table 3).

Patients with an abnormal stress response had a poorer endpoint-free survival (Figure 1, p<0.001). A significantly lower relative decrease in RVESV during stress was observed in endpoint patients compared to patients who did not reach the study endpoint (-17±15 vs-26±13 %, p=0.045).

In figure 2 the endpoint-free survival for the patients with the largest (≥-25%) and lowest (<-25%) relative decrease in RVESV during stress is shown. Patients with a larger relative decrease during stress experienced a better endpoint-free survival (p=0.044).

Determinants of the composite endpoint

Univariable analysis showed that patients were significantly more likely to experience the composite endpoint when they had an abnormal stress response (HR: 10.5; 95% CI 248-44.78), higher NTproBNP levels (HR: 1.03; 95% CI 1.00-1.05), or a higher relative

Table 2. Clinical state at latest follow-up

	Patients (n=100)
Median age at latest follow-up (years)	29.4 (24.3–39.7)
Median time after dobutamine CMR (years)	8.6 (6.7–14.1)
Composite endpoint (n, %)	10 (10.0)
Median time after dobutamine CMR (years)	6.2 (3.1–13.3)
Median time after TOFr (years)	26.0 (17.1–37.2)
Ablation/cardioversion of arrhythmias (n, %)	5 (5.0)
Atrial arrhythmia (n, %)	3 (3.0)
Ventricular arrhythmia (n, %)	2 (2.0)
ICD after VT (n, %)	1 (1.0)
VO_2 max ≤65% of predicted (n, %)	4 (4.0)

Results are given as median (IQR) or as counts (percentages).
Abbreviations; CMR: cardiac magnetic resonance imaging, TOFr: Tetralogy of Fallot repair, ICD: implantable cardioverter defibrillator, VT: Ventricular tachycardia, VO_2: oxygen uptake.

decrease in RVESV during stress (HR: 1.06; 95% CI 1.01–1.12), see Table 4. There was no-statistical significant correlation between NTproBNP levels and relative change in RVESV during stress, r=0.06, p=0.54.

In a multivariable model with both NTproBNP and relative change in RVESV, both parameters remained predictive for the composite endpoint. In a multivariable model with NTproBNP and abnormal stress response, NTproBNP lost its predictive value for the composite endpoint however abnormal stress response remained a strong independent predictor for the composite endpoint, see Table 5.

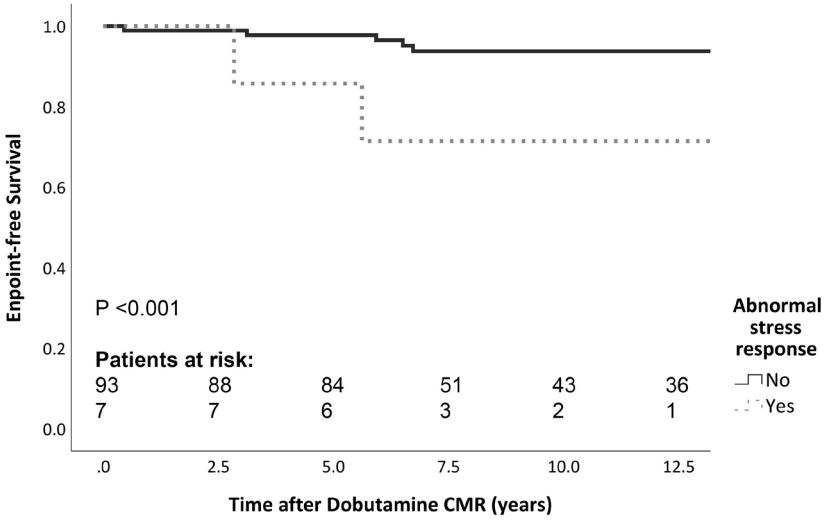
Discussion

In this study we demonstrated, despite a relatively low number of endpoints, a clear relation between ventricular response to low-dose dobutamine stress CMR and a composite endpoint in TOF patients mid-term after TOF-repair. An abnormal response to dobutamine stress and a diminished relative decrease in RVESV during stress were associated with adverse outcome.

Patients with TOF are at increased risk of mortality and morbidity.[1, 2, 4, 5] Many of the studies that have looked at predictors in TOF patients have been performed in in older patients cohorts with an older age at initial repair.[4, 7-9, 12, 13, 24] What our current study adds, in a cohort of adolescents and young adults (median age 17.8 years), is that stress CMR is more predictive for poor outcome after 8.6 years follow-up than conventional CMR imaging parameters. Also the median age at TOF-repair in our cohort was 0.9 years, which is highly comparable to the clinical practice for the past two decades.[25, 26]

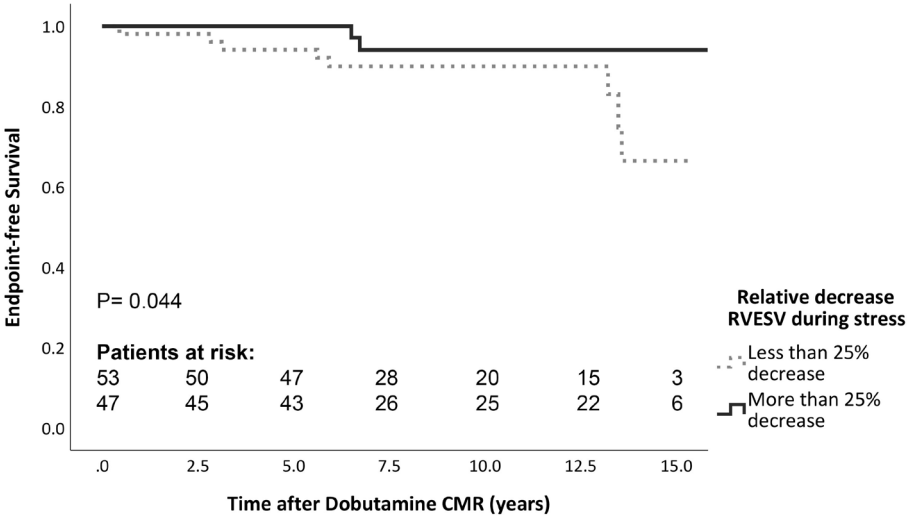
In other studies, several predictors for outcome have been described.[4, 8, 9, 12, 24, 27]

Figure 1. Endpoint-free survival for normal vs abnormal dobutamine stress response



Abbreviations: CMR; cardiac magnetic resonance imaging.

Figure 2. Endpoint-free survival for the relative decrease of RVESV during stress



Abbreviations: RVESV: right ventricular end systolic volume, CMR; cardiac magnetic resonance imaging.

Clinical and non-imaging parameters

Of the non-imaging derived parameter, NT-proBNP, QRS-duration and peak VO_2 are related to outcome in TOF.[4, 8, 9] In an adult congenital heart disease (CHD) cohort, a NT-proBNP level of >33 µmol/L identified patients with increased risk for poor outcome.[28] Also in adult TOF patients elevated NT-proBNP levels are related to adverse clinical outcome.[8] Although the median NT-proBNP levels in our study were relatively low (12.9 µmol/L). We observed that higher NTproBNP levels were associated with the composite endpoint in univariable analysis and in a multivariable model with relative change in RVESV. In a multivariable model with abnormal stress response NTproBNP lost its predictive value for the composite endpoint, however a strong trend (p=0.055) remained.

QRS duration ≥180 ms in adults and ≥170 ms in children are known predictors for ventricular tachycardia and sudden death.[4, 29] In our relatively young TOF cohort, we observed no differences in QRS duration between the patients with and without a composite endpoint. Only three patients had a QRS duration >170 ms.

Peak VO_2 is an established prognostic marker in CHD patients and TOF patients and guidelines recommend cardio-pulmonary exercise testing during routine follow-up of TOF patients.[9, 10, 26, 27, 30] Diller *et al*.[10] reported in 2005 that older (31.8 years) TOF patients with a peak VO_2 of ≤15.5 ml/kg/min have an increased risk of hospitalization and death during follow-up. Giardini *et al*.[31] observed that a lower peak VO_2 is associated with death and hospitalization during follow-up. In another larger and relatively young (25.5 years) TOF cohort, a peak VO_2 ≤65% of predicted was associated with an increased risk for death, sustained ventricular tachycardia and cardiac related hospitalizations.[9]

As mentioned, research in CHD patients is complicated by the relatively low incidence of hard endpoints, resulting in the use of surrogate endpoints.[14] Based on the relations between exercise performance, particularly VO_2 max and subsequent outcome, peak VO_2 ≤65% was included in the composite endpoint used in our study.

RV size and function

Alongside clinical parameters, RV size is a key factor in outcome in TOF and the decision for PVR. If PVR is performed on time, i.e. before irreversible remodeling has occurred, it might help to normalize volumes and improve function. However, survival benefit of PVR using the current criteria has not been demonstrated.[5, 14, 32, 33] International guidelines indicate that several factors such as the presence of symptoms, degree of PR, RVEDV, RVESV and objective exercise performance can be used to determine if PVR is justified.[14, 26, 30] However, often no quantitative limits are given and the criteria differ between guidelines.[26, 30] Also, RV size parameters fail to take into consideration the underlying RV mechanics, such as contractility, diastolic function, energy loss, ventriculo-arterial coupling (VA coupling) or ventricular function during stress.[21, 34-36] Contractility can be maintained in severe RV dilatation.[35] Diastolic RV function is impaired in many TOF patients and relates to clinical state, but has not been shown to predict poor outcome.[37] Latus *et al*.[35] showed that RV-Pulmonary arterial (PA) coupling is impaired

Table 3. CMR parameters for patients with and without a composite endpoint

	All patients (n=100)		**Composite endpoint (n=10)**		**No composite endpoint (n=90)**		**P-value event vs no event in stress**
	Rest	*Stress*	*Rest*	*Stress*	*Rest*	*Stress*	
Rest CMR							
LV EDV (ml/m^2)	80±13	78±14*	84±15	84±14	79±12	77±14*	0.15
ESV (ml/m^2)	33±9	22±8*	35±10	26±12*	33±8	22±8	0.12
SV (ml/m^2)	47±8	55±9*	49±10	58±8*	46±8	55±9*	0.34
EF (%)	59±7	72±7*	58±8	70±9*	59±7	72±7*	0.34
RV EDV (ml/m^2)	130±39	125±38*	123±43	121±35	130±39	126±38*	0.70
ESV (ml/m^2)	67±26	51±23*	58±26	47±22*	68±26	51±23*	0.64
SV (ml/m^2)	63±17	75±20*	65±22	74±20*	62±17	75±20*	0.86
EF (%)	49±7	61±8*	51±5	62±8*	49±8	61±9*	0.60
Mass volume ratio (g/ml)	0.18±0.05		0.18±0.04		0.19±0.05		0.86
PR (%)	29 (10-44) (n=95)	30 (10-44) (n=80)	17 (9–27) (n=10)	17 (6–32) (n=9)	32 (9–45) (n=85)	33 (11–46) (n=71)	0.14
Abnormal stress response (n, %)	7 (7.0)		3 (30.0)		4 (4.4)		0.021
Relative change during stress							
LV EDV (%)		-3±9		0±6		-3±9	0.22
ESV (%)		-35±14		-27±16		-36±14	0.062
SV (%)		20±15		22±17		20±15	0.74
EF (%)		24±12		21±15		24±11	0.43
RV EDV (%)		-3±9		2±11		-3±9	0.13
ESV (%)		-25±13		-17±15		-26±13	0.045
SV (%)		21±17		18±18		21±17	0.61
EF (%)		24±13		17±12		25±13	0.052

Results are given as mean (SD) or as median (IQR) or as counts (percentages).
No statistical significant differences at rest between the group with and without a composite endpoint, no significant differences were found.
* indicates a statistical significant difference between rest vs stress within the subgroup.
Abbreviations; CMR: Cardiovascular magnetic resonance, LV: left ventricle, EDV: end diastolic volume, ESV: end systolic volume, SV: stroke volume, EF: ejection fraction, RV: right ventricle, PR: pulmonary regurgitation.

Table 4. Univariable cox-regression analyses for the composite endpoint

	Univariable analysis		
	HR	*95% CI*	*P-value*
Age at CMR (years)	1.01	0.95–1.07	0.74
NT-proBNP (µmol/l)	1.03	1.00–1.05	0.030
QRS duration (ms)	1.01	0.99–1.04	0.41
Rest CMR			
LVEDV (ml/m^2)	1.02	0.97–1.08	0.43
LVESV (ml/m^2)	0.86	0.93–1.09	0.86
LVEF (%)	1.01	0.92–1.11	0.82
RVEDV (ml/m^2)	0.99	0.97–1.01	0.22
RVESV (ml/m^2)	0.98	0.95–1.01	0.094
RVEF (%)	1.04	0.95–1.04	0.83
RV mass volume ratio (g/ml) (↑0.1)	1.40	0.32-6.02	0.65
Relative change during stress			
LVESV (%)	1.04	0.99–1.09	0.086
LVEF (%)	0.98	0.92–1.04	0.42
RVEDV (%)	1.07	1.01–1.15	0.036
RVESV (%)	1.06	1.01–1.12	0.016
RVEF (%)	0.94	0.89–0.99	0.043
Abnormal stress response	10.5	2.48–44.78	0.001

Abbreviations; CMR: cardiac magnetic resonance imaging, LV: left ventricle, RV: right ventricle, EDV: end diastolic volume, ESV: end systolic volume, SV: stroke volume, EF: ejection fraction.

in TOF patients at rest and did not improve with dobutamine stress. In patients without a transannular patch, RV-PA coupling did improve with dobutamine stress.[35] Whether these findings relate to our and observations of others of impaired reduction of RVESV with dobutamine stress,[18] is not certain at present.

It is important to identify parameters for early RV dysfunction that have prognostic impact. The cardiac response to dobutamine stress could be an additional parameter in this decision process, combining volumetric and functional parameters with a state of stress, unmasking abnormalities only visible during stress.[21]

Stress CMR

Previous studies using low-dose dobutamine stress CMR, demonstrated that TOF patients are able to decrease ESV and increase EF during stress. Some studies also describe an abnormal decrease in RVEDV.[16-18, 21] In a 5-year follow-up study of TOF patients, our group previously showed that patients with a small relative increase in RVEF during dobutamine stress were more likely to have a large decrease in peak VO_2

Table 5. Multivariable cox-regression analyses for the composite endpoint

	multivariable analysis		
	HR	*95% CI*	*P-value*
Multivariable model 1			
NT-proBNP (µmol/l)	1.0	1.0–1.1	0.055
Abnormal stress response	10.4	2.5–43.7	0.001
Multivariable model 2			
NT-proBNP (µmol/l)	1.0	1.0–1.1	0.009
Relative change in RVESV (%)	1.1	1.0–1.1	0.004

Abbreviations; CMR: cardiac magnetic resonance imaging, LV: left ventricle, RV: right ventricle, EDV: end diastolic volume, ESV: end systolic volume, SV: stroke volume, EF: ejection fraction.

five years later.[17] However the relationship between stress response and cardiac events has not been described yet in TOF patients.

In systemic RV patients with a biventricular circulation, a previous study identified that an abnormal stress response (present in 17 of the 39 patients) was predictive for cardiac events during follow-up.[20] We observed an abnormal stress response in only seven patients, most likely explained by the differences in age and type of CHD. However, these seven patients experienced more often an adverse outcome during follow-up and had a worse endpoint-free survival.

In young Fontan patients, without other known parameters predictive for cardiac events, the relationship between single ventricle functional reserve (EF_{stress}-EF_{rest}) and events has recently been described by our group.[19] In our current TOF study, the relative decrease of RVESV during stress was also associated with the composite endpoint. All these studies mentioned above indicate that dobutamine stress imaging may be helpful in risk stratification and predicting future events.

Limitations

Although the absolute number of TOF patients receiving a dobutamine CMR is the largest reported cohort so far, the number of hard endpoints during follow-up was limited, which is a known limitation in CHD research.[14] We therefore used a composite endpoint of cardiac death, arrhythmias and diminished exercise tolerance to assess the possible association between the stress CMR and subsequent adverse outcome. Relatively few patients reached this composite endpoint, which is a limitation of our study. However, despite the small number of endpoints obtained, we observed a clear relationship between the ventricular stress response and subsequent outcomes during follow-up. Information on how to interpret stress CMR in TOF patients was not available at the time of stress CMR and therefore stress CMR parameters were not used for clinical decision making.

Secondly, it is not certain whether dobutamine stress CMR gives the same results as exercise stress CMR. Because our CMR scanner is not suitable for supine leg exercise, the effects of exercise on cardiac function had to be simulated with pharmacological stress. Thirdly, LGE or T1 mapping could not be performed because of time constraints during the extensive scan protocol. Both factors are associated with outcome in TOF patients.[38, 39]

Conclusion

An abnormal ventricular response to dobutamine stress is associated with adverse outcome in young TOF patients.

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Chapter 10

Associations between blood biomarkers, cardiac function and adverse outcome in a young Tetralogy of Fallot cohort

In preparation

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Abstract

Aims

To determine the potential prognostic value and clinical correlations of blood biomarkers in a cohort op patients with Tetralogy of Fallot (TOF).

Methods

In multicentre prospective studies TOF patients underwent blood sampling, cardiopulmonary exercise testing and low-dose dobutamine stress cardiac magnetic resonance (CMR) imaging. Several biomarkers including NT-proBNP, GDF-15, Galectin-3, ST-2, DLK-1, FABP4, IGFBP-1, IGFBP-7, MMP-2, and vWF were assessed in the blood sample. During subsequent follow-up, patients were assessed for reaching the study endpoint (cardiac death, arrhythmia-related hospitalization or cardioversion/ablation, VO_2 max ≤65% of predicted). Regression analysis was used to explore the correlation between the biomarkers (corrected for age and gender) and other clinical parameters. The potential predictive value of blood biomarkers and events were assessed with Kaplan-Meier analysis and Cox proportional hazard analysis.

Results

We included 137 Fallot patients, median age 19.2 (Interquartile range: 14.6–25.7) years, median age at TOF-repair 0.9 (0.5–1.9) years. After a median follow-up of 8.7 (6.3–10.7) years, 20 (14.6%) patients reached the composite endpoint. In univariable cox-regression analysis elevated NT-proBNP levels were associated with the composite endpoint. In a multivariable cox-regression analysis corrected for age at study baseline, elevated IGFBP-7 and MMP-2 levels were associated with the composite endpoint. The event-free survival was worse for patients with higher IGFBP-7 levels (p=0.014). There was also a correlation (β=-0.27, p=0.010) between DLK-1 and relative change in right ventricular end systolic volume during dobutamine stress CMR.

Conclusions

NT-proBNP, IGFBP-7, MMP-2 and DLK-1 levels are related to cardiac function and long-term outcome in TOF patients.

Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease (ConHD).[1] Nowadays survival after surgical repair is good with long-term survival-rates of 95% at 10-year and >90% at 25.[1-3]

Despite good survival-rates, patients experience long-term problems, mainly related to residual pulmonary regurgitation (PR).[1] Right ventricular dilatation, ventricular dysfunction and arrhythmias are common at long-term follow-up.[2, 4-7]

Peak oxygen uptake (VO_2), QRS duration and cardiac magnetic resonance imaging (CMR) parameters have been associated with adverse outcome, often in older cohorts of TOF patients.[8-11] Nonetheless, additional parameters are needed to better identify patients at risk for adverse outcome. This search is hampered by long symptom-free intervals and therefore surrogate outcome markers are often used.[12, 13]

Blood biomarkers are a potential tool in risk stratification in ConHD patients. In recent years a number of pathways and related blood biomarkers of myocardial fibrosis, remodeling and vascularization have been discovered, mostly in adult acquired heart disease patients.[14-18] However in young TOF patients relatively few biomarkers have been studied. Therefore, the aim of this study was to explore the value of several promising biomarkers in a relatively young TOF cohort.

Methods

Patients

We included all TOF patients with at least 5 year follow-up after TOF-repair of whom blood samples were stored in the setting of cross-sectional and prospective studies in five tertiary referral centers between 2002 and 2018.[19-21] Patients with contra-indications for CMR were excluded.

The institutional review boards approved the studies. All participants, and if necessary their parents, gave written informed consent before inclusion in these studies. At the baseline study assessment all patients underwent blood sampling, CMR and cardiopulmonary exercise testing (CPET) according to a standard protocol. The patients were subsequently followed in the setting of usual care.

Blood sample analysis

Blood samples were taken from a peripheral vein and collected in EDTA tubes. Samples were stored at −80°C. The frozen samples were shipped to Olink Proteomics AB (Uppsala, Sweden) for analysis with the Olink Cardiovascular panel III. Using proximity extension assay (PEA) technology the levels of biomarkers were measured, this PEA technique has been described extensively before.[22] All blood samples were coded, therefore the laboratory staff was blinded for the patients clinical and study data. The biomarker values are presented as normalized protein expression (NPX) units on a Log2 scale.

For the aim of the current study, we examined ten biomarkers that have been associated with ConHD, TOF, cardiac fibrosis or heart failure in general.[16, 23-28] These biomarkers were: NT-proBNP, GDF-15, Galectin-3, ST2, DLK-1, FABP-4, IGFBP-1, IGFBP-7, MMP-2, and vWF. The biomarkers were selected prior to the data analysis.

CMR acquisition and analysis

All participants underwent CMR on the locally available scanners with dedicated phased-array cardiac surface coils. All images were obtained during breath-hold. CMR imaging was performed at rest and repeated during continuous infusion of low-dose (7.5 μg/kg/min) dobutamine hydrochloride (Centrafarm Services, Etten-Leur, the Netherlands). The dobutamine infusion was decreased (or stopped if necessary) when the heartrate increased >50%, if the systolic and/or diastolic blood pressure increased >50% or decreased >20%, if serious arrhythmias occurred, or if a patient did not tolerate the dobutamine effect. Technical details on our rest and dobutamine stress protocol have been published previously.[19-21, 29]

Analysis were performed with the software packages MASS and FLOW (Medis Medical Imaging Systems, Leiden, the Netherlands). Contours were manually drawn in end-diastole and end-systole, papillary muscle and trabeculae were excluded from the blood pool. All CMR's were analysed by one of the authors (EvdB) under supervision of one of the authors (WH) with longstanding experience in CMR. Biventricular end diastolic volume (EDV) and end systolic volume (ESV) were obtained and used to calculate the ejection fraction (EF). All ventricular volumes were indexed (i) for body surface area.

Relative changes in CMR parameters during stress were calculated as follows: relative $parameter_{change}$ = [($parameter_{stress}$ − $parameter_{rest}$)/$parameter_{rest}$]*100.

Cardiopulmonary exercise tests

Cardiopulmonary exercise tests (CPETs) were performed on a bicycle ergometer according to protocols that were used in previous studies by our group.[19-21] From these exercise tests the VO_2 peak was assessed and expressed as percentage of predicted values. Exercise tests with a peak respiratory exchange rate (RER peak) of ≥1.0 were included in the analysis.

Composite study endpoint

After the baseline study assessment, patients received regular patient specific care. For the purpose of the current study the medical records of the latest outpatients visit were reviewed and all cardiac events during follow-up were recorded until June 2019. The survival status of the patients was checked in the Municipal Population Register.

The study endpoint was defined as a composite of cardiac death, hospitalization for arrhythmias or cardioversion/ablation for arrhythmias or reaching a CPET VO_2 max below 65% (due to cardiac reasons) during follow-up (after the initial baseline study CPET).[11, 13, 30]

Statistical methods

Continuous variables with a normal distribution were summarized as mean (SD). Differences between patients with and without events, between dominant ventricles and Fontan technique were analysed using the Student's t-tests. Variables with a non-normal distribution were presented as median (25-75th percentile), and between-group differences were analysed by Mann-Whitney U tests. Categorical variables were presented as numbers and percentages, whereas between-group differences were evaluated by chi-squared tests. In regression analysis we assessed correlations between several clinical parameters and the Olink biomarkers, adjusted for gender and age.

The endpoint-free survival were estimated by Kaplan–Meier curves and differences between patients groups, defined by the level of biomarkers, were evaluated using the log-rank test. We applied Cox proportional hazard regression analyses to explore the association between the biomarkers and the endpoint-free survival. In the Cox-model we used z-scores (the standardized form) of the Olink biomarkers. We analysed the crude Cox-model (univariable analysis of the standardized Olink biomarker) and a Cox-model corrected for age.

All analyses were performed using SPSS statistical software package version 24.0 (IBM Corp. in Armonk, NY, USA), a two-sided p-value <0.05 was considered statistically significant.

Results

The blood samples of 138 patients were shipped for analysis. The available biomarker was successfully analysed in 137 patients, in one patient the blood sample was of insufficient quality. This patients was excluded from the study. At baseline a CMR was performed in all 137 patients and an adequate CPET was performed in 108 patients.

The median age at the baseline study assessment was 19.2 years (14.6 – 25.7), median 17.3 years (13.9 – 23.8) after the TOF-repair. Table 1 shows the patient characteristics and CMR and CPET parameters for all patients and the patients who did and did not reach the composite endpoint.

Composite endpoint and baseline characteristics

During a median follow-up of 8.7 (6.3 – 10.7) years, 20 (14.6%) reached the composite endpoint median 6.0 (1.8 – 8.1) years after the baseline study measurement (Table 2). All patients were alive at latest follow-up. A total of 13 (9.5%) patients developed an arrhythmia and 7 (5.1%) patients reached a VO_2 max ≤65% of predicted. Patients who reached the composite endpoint were significantly older at the baseline study measurement, 29.6 vs 19.2 years, p=0.040. Patients who reached the composite endpoint had a higher left ventricular (LV) mass, a higher LVSV and a higher RVEF, see Table 1.

Table 1. Baseline patient characteristics for patients with and without a composite endpoint

	Patients (n=137)	Composite endpoint (n= 20)	No composite endpoint (n=117)	P-value
Male (n, %)	92 (67.2)	12 (60.0)	80 (68.4)	0.45
22q11 (n, %)	5 (3.6)	1 (5.0)	4 (3.4)	0.55
Age at study (years)	19.2 (14.6 – 25.7)	29.6 (14.6 – 52.3)	19.0 (14.6 - 24.2)	0.040
Time after TOF repair (years)	17.3 (13.9 – 23.8)	25.9 (14.0 – 41.4)	17.1 (13.7 – 22.4)	0.035
Length (cm)	168 ± 14	167 ± 14	169 ± 14	0.59
Weight (kg)	62.7 ± 17.4	62.7 ± 18.9	62.7 ± 17.3	1.00
BSA (m^2)	1.70 ± 0.30	1.69 ± 0.32	1.70 ± 0.29	0.88
QRS duration (ms)	133 ± 24	142 ± 27	132 ± 24	0.087
Palliative shunt (n, %)	31 (22.6)	8 (40.0)	23 (19.7)	0.078
Age at TOF-repair (years)	0.9 (0.5–1.9	1.9 (0.4 – 10.6)	0.9 (0.5 – 1.7)	0.097
Transannular patch (n, %)	92 (67.2)	12 (60.0)	80 (68.4)	0.45
PVR at baseline (n, %)	18 (13.1)	1 (5.0)	17 (14.5)	0.47
Maximal exercise parameters	n= 108	n= 15	n= 93	
VO_2 max (ml/min/kg)	36.5 ± 8.1	35.1 ± 7.8	36.7 ± 8.2	0.45
VO_2 max (% of predicted)	86.4 ± 18.5	92.5 ± 21.0	85.4 ± 18.0	0.17
Rest CMR	n=137	n=20	n=117	
LV EDV (ml/m^2)	84 ± 13	88 ± 14	83 ± 12	0.11
ESV (ml/m^2)	35 ± 8	34 ± 9	35 ± 8	0.82
SV (ml/m^2)	50 ± 8	54 ± 8	49 ± 8	0.005
EF (%)	59 ± 6	62 ± 7	59 ± 6	0.063
Mass (g/m^2)	53 ± 11	58 ± 13	53 ± 10	0.031
Mass/ EDV ratio (g/ml)	0.63 ± 0.13	0.66 ± 0.11	0.64 ± 0.12	0.47
RV EDV (ml/m^2)	129 ± 35	124 ± 38	129 ± 34	0.53
ESV (ml/m^2)	64 ± 23	57 ± 24	66 ± 22	0.11
SV (ml/m^2)	65 ± 16	67 ± 18	64 ± 16	0.44
EF (%)	51 ± 7	55 ± 7	50 ± 7	0.002
Mass (g/m2)	26 ± 10	27 ± 10	26 ± 10	0.84
Mass/ EDV ratio (g/ml)	0.21 ± 0.10	0.22 ± 0.07	0.21 ± 0.10	0.63
PR (%)	28 (10 – 41) (n=128)	21 (1 – 29) (n=20)	31 (13 - 43) (n=108)	0.027
Relative change during stress	n= 71	n= 9	n= 62	
LV EDV (%)	-3 ± 9*	-3 ± 10	-3 ± 9*	0.93
ESV (%)	-34 ± 16*	-33 ± 14*	-34 ± 15*	0.80
SV (%)	19 ± 15*	18 ± 16*	19 ± 15*	0.81
EF (%)	22 ± 11*	21 ± 12*	22 ± 11*	0.83
RV EDV (%)	-5 ± 10*	-7 ± 12	-7 ± 12*	0.34
ESV (%)	-29 ± 16*	-20 ± 18*	-29 ± 16*	0.80
SV (%)	19 ± 18*	12 ± 13*	20 ± 18*	0.22
EF (%)	26 ± 15*	23 ± 14*	26 ± 15*	0.60

Results are given as mean (standard deviation), as median (range) or as counts (percentages).
*indicates a significant difference between the rest and stress measurement.
Abbreviations; BSA: body surface area, CMR: cardiovascular magnetic resonance imaging, EDV: end diastolic volume, EF: ejection fraction, ESV: end systolic volume, LV: left ventricle, RV: right ventricle, SV: stroke volume, VO_2 max: maximum oxygen uptake.

Table 2. Clinical state at latest follow-up

	Patients (n=137)
Median age at latest follow-up (years)	26.8 (22.7 - 37.1)
Median time after study (years)	8.7 (6.3 - 10.7)
Composite endpoint (n, %)	20 (14.6)
Median time after baseline study (years)	6.0 (1.8 - 8.1)
Median time after TOF-repair (years)	32.2 (19.9 - 45.3)
Arrhythmias (n, %)	13 (9.5)
Atrial arrhythmia (n, %)	6 (4.4)
Ventricular arrhythmia (n, %)	5 (3.6)
AV block (n, %)	2 (1.5)
VO_2 max ≤ 65% of predicted (n, %)	7 (5.1)

Abbreviations; TOF: Tetralogy of Fallot, VO_2 max: maximum oxygen uptake.

Composite endpoint and biomarkers

Table 3 shows the Cox-regression analysis. A 1-SD increase of IGFBP-7 (Hazard ratio (HR): 1.71/ 1-SD, 95% CI: 1.11 -2.63) and NT-proBNP (HR: 1.82/ 1-SD, 95% CI: 1.15 -2.90) were associated with the composite endpoint during follow-up. However, corrected for age at study baseline, NT-proBNP lost its predictive value for the composite endpoint. In the multivariable analysis higher levels of IGFBP-7 and MMP-2 were associated with the composite endpoint during follow-up.

Figure 1 shows the endpoint-free survival of patients with the highest and lowest IGFPB-7 levels (p=0.014).

Association biomarkers with other clinical parameters

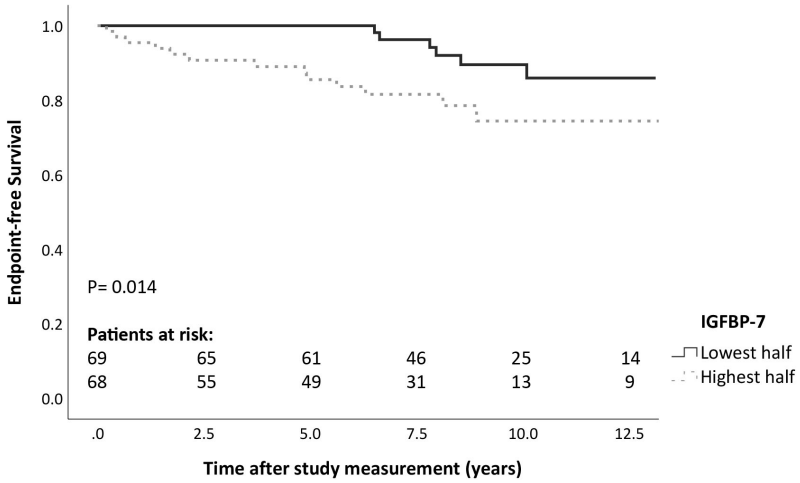
In Table 4 associations, corrected for age and gender, between the biomarkers and several baseline CMR and CPET parameters are shown. We observed a significant association between DLK-1 levels and the relative decrease in RVESV during dobutamine stress. DLK-1 decreased with a factor β= -0.27 for every percent less decrease in RVESV during stress.

Table 3. Cox-regression analyses for biomarkers and their relation to the composite endpoint.

	Crude univariable model			Model adjusted for age at study		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Levels (per 1 SD increase)						
DLK-1	1.05	0.68 – 1.61	0.83	1.11	0.73 - 1.69	0.63
FABP4	1.20	0.80 – 1.81	0.37	0.84	0.53 - 1.32	0.44
Gal-3	1.60	0.93 – 2.75	0.092	1.10	0.64 - 1.88	0.73
GDF-15	1.12	0.80 – 1.57	0.52	0.70	0.34 - 1.43	0.32
IFGBP-1	1.25	0.80 - 1.96	0.33	1.43	0.95 - 2.17	0.088
IFGBP-7	**1.71**	**1.11 - 2.63**	**0.014**	**1.54**	**1.03 - 2.31**	**0.035**
MMP-2	1.54	0.97 - 2.46	0.066	**1.68**	**1.03 - 2.74**	**0.039**
NT-proBNP	**1.82**	**1.15 - 2.90**	**0.011**	1.42	0.88 - 2.28	0.15
ST2	0.97	0.63 - 1.49	0.89	0.95	0.47 - 1.91	0.88
vWF	1.25	0.86 - 1.82	0.24	1.10	0.71 - 1.72	0.67

Abbreviations; CI: confidence interval, DLK-1: protein delta homolog 1, FABP4: Fatty acid-binding protein 4, Gal 3: galectin 3, GDF-15: growth differentiation factor 15, HR: hazard ratio, IGFBP1: insulin-like growth factor-binding-protein 1, IGFBP-7: insulin-like growth factor-binding protein 7, MMP-2: matrix metalloproteinase-2, NT-proBNP: N-terminal pro-brain natriuretic peptide, ST2: suppression of tumorigenicity 2, vWF: von Willebrand factor.

Figure 1. Kaplan-Meier curves for endpoint-free survival for the lowest versus highest half of IGFBP-7.



Abbreviations; IGFBP-7: insulin like growth factor binding protein 7.

Table 4. Association between study parameters and biomarker levels, corrected for age and gender

		Independent variable		
Dependent variable		**Max VO_2 max (per 1 ml/min/kg)**	**RVEF (Per 1%)**	**Relative decrease in RVESV during stress (per %)**
	β	-0.10	-0.03	-0.27
DLK-1	95% CI	-0.03 – 0.01	-0.02 – 0.01	-0.02 - -0.003
	p-value	0.35	0.75	0.010
	β	-0.41	-0.09	-0.14
FABP4	95% CI	-0.05 – -0.02	-0.03 – 0.001	-0.02 – 0.004
	p-value	<0.001	0.25	0.24
	β	-0.01	0.08	0.08
Gal-3	95% CI	-0.01 – 0.01	-0.01 – 0.02	-0.03 – 0.01
	p-value	0.91	0.34	0.50
	β	-0.10	0.03	-0.02
GDF-15	95% CI	-0.02 – 0.01	-0.01 – 0.02	-0.01 – 0.01
	p-value	0.30	0.72	0.84
	β	0.18	0.07	0.17
IGFBP-1	95% CI	-0.01 – 0.06	-0.02 – 0.04	-0.01 – 0.03
	p-value	0.10	0.42	0.17
	β	0.03	-0.08	0.03
IGFBP-7	95% CI	-0.01 – 0.01	-0.02 – 0.01	-0.01 – 0.01
	p-value	0.77	0.33	0.83
	β	-0.04	0.01	0.11
MMP-2	95% CI	-0.01 – 0.01	-0.01 – 0.01	-0.003 – 0.01
	p-value	0.69	0.89	0.38
	β	-0.03	0.09	0.08
NT-proBNP	95% CI	-0.03 – 0.02	-0.01 – 0.04	-0.08 – 0.02
	p-value	0.74	0.30	0.51
	β	-0.05	-0.12	-0.06
ST2	95% CI	-0.02 – 0.01	-0.02 – 0.01	-0.01 – 0.01
	p-value	0.67	0.16	0.62
	β	-0.03	0.03	0.06
vWF	95% CI	-0.03 – 0.02	-0.02 – 0.03	-0.01 – 0.02
	p-value	0.75	0.74	0.58

Interpretation: for every increase %, the biomarker increases or decreases with factor β.
Abbreviations; CMR: cardiovascular magnetic resonance imaging, EDV: indexed end diastolic volume, EF: ejection fraction, DLK-1: protein delta homolog 1, FABP4: Fatty acid-binding protein 4, Gal 3: galectin 3, GDF-15: growth differentiation factor 15, IGFBP1: insulin-like growth factor-binding protein 1, IGFBP-7: insulin-like growth factor-binding protein 7, MMP-2: matrix metalloproteinase-2, NS; not significant, NT-proBNP: N-terminal pro-brain natriuretic peptide, ST2: suppression of tumorigenicity 2, VO_2 peak: maximum oxygen uptake, vWF: von Willebrand factor.

Discussion

In this study in relatively young TOF patients we demonstrated an association between several blood biomarkers (NT-proBNP, MMP-2, FABP-4, IGFBP7 and DLK-1) and clinical condition, cardiac function and events during 8 years of follow-up.

Patients with TOF have an increased risk of arrhythmias, impaired exercise capacity, diminished ventricular function and mortality during follow-up. Several predictors for these adverse events are known, such as peak VO_2, QRS duration and CMR parameters like RVEF, LVEF and RV mass volume ratio.[8-11, 31, 32] However, many of these studies have been performed in older TOF patients operated at an older age than has been common practice more recently.[4, 9, 10, 33, 34] Risk-stratification is necessary to identify young TOF patients at risk for deterioration. Assessment of blood biomarker levels is a relatively simple method that may be used to monitor clinical condition.

There may be differences in pathways involved in heart/ circulatory failure in children with ConHD compared to adults with heart failure, including adults with ConHD.[17, 18, 35] As such, our study explored pathways involved in the maintenance of cardiac function and long-term outcome of relatively young TOF patients. The processes leading to myocardial changes to adapt to chronic abnormal loading conditions in ConHD have been incompletely understood.[35, 36] Pathways most likely involved in the development of heart failure in ConHD are related to hypertrophy, fibrosis, remodelling, vascularization, inflammation, cardiac metabolism and repair.[35] In this study we examined ten biomarkers that have been associated with ConHD, TOF, cardiac fibrosis or heart failure in general.[16, 23-28] We will subsequently discuss the biological role of these biomarkers and associations with clinical outcomes in our study.

NT-proBNP

In response to increased myocardial stress and ventricular volume and pressure overload, NT-proBNP is secreted.[37] It is a well-known biomarker in acquired heart failure and adult ConHD patients; elevated NT-proBNP levels are associated with mortality and adverse events.[17, 37-39]

In TOF patients, Westhoff-Bleck *et al*.[9] observed that higher NT-proBNP levels were associated with the severity of PR and adverse outcomes. In our study, NT-proBNP levels were associated with the composite endpoint in univariable analysis. However, when corrected for age at baseline NT-proBNP lost its predictive value. A possible explanation for the different relation between NT-pro BNP levels and outcome is the relative young age at baseline (19.2 years vs 26.3 years) and at TOF-repair in our cohort (0.9 vs 2.5 years) compared to the cohort of Westhoff-Bleck et al.[9]

IGFBP-7

IGF binding proteins (IGFBPs) are a family of proteins that regulate and modulate IGF activity and have indirect effects on growth hormone.[40] IGFBP-7 is highly expressed in endothelial cells and has been linked to collagen deposition.[41-43] Interestingly, IGFBP-7

has been linked to post infarction myocardial repair.[44] IGFBP-7 has been identified as a potential biomarker for adverse outcome in acquired heart failure patients,[26] and is associated with diastolic dysfunction and lower VO_2 max.[42] In ConHD patients, the role of IGFPBs in cardiac function or prognosis is largely unexplored, but has been linked to general growth, failure to thrive and nutritional status.[45, 46]

In young Fontan patients we also observed an association between IGFPB-7 levels (corrected for age and gender) and cardiac function and VO_2 max (manuscript accepted). In our current study we found that higher IGFBP-7 levels with adverse outcomes. These observations indicate a possible role of IGFBP-7 in the follow-up of TOF patients and perhaps other types of ConHD.

MMP-2

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases and are controlled through tissue inhibitors of metalloproteinases (TIMPs).[47] MMPs can degrade components of the extra cellular matrix (ECM) including collagens and play and important role in ECM remodelling.[48-50] In rat, canine and ovine models of acute pulmonary embolism pre-treatment with doxycycline -a non-selective MMP inhibitor- reduced RV dilation.[50]

In patients with congestive heart failure, higher MMP-2 levels have been associated with higher NYHA class, older age and with hospitalization for heart failure during subsequent follow-up.[49] In adult patients with hypertrophic cardiomyopathy higher levels of MMP-2 have been associated with LV systolic dysfunction.[51] In a large ConHD cohort Baggen *et al*.[24] have observed an association between MMP-2 levels and exercise capacity.

In TOF patients MMP-9 is thought to have a modulating effect on aortic stiffness and aortic root dilatation.[52] We observed that elevated MMP-2 levels, corrected for age at study, were associated with an increased risk for the composite endpoint.

DLK-1

DLK-1 is part of the epidermal growth factor-like family and plays a role in muscular differentiation, angiogenesis, and fibrosis.[16, 53] DLK-1 knock-out mice display an increased collagen deposition, LV dilatation and reduced myocardial contractility.[16] In human ischemic myocardial tissue DLK-1 mRNA expression was down-regulated compared to healthy tissue.[16]

Recently we observed that young Fontan patients with higher DLK-1 levels have a better severe event-free survival (manuscript accepted) and a higher functional reserve (EF_{stress}– EF_{rest}) during dobutamine stress CMR, which is a predictor for outcome.[54] In the current study in TOF patients we also observed an association between DLK-1 levels and the response to dobutamine stress CMR. Higher DLK-1 levels were associated with a larger relative decrease in RVESV during stress. Recently an impaired relative decrease in RVESV during stress has been linked to adverse outcome.[13]

FABP-4

FABP-4 is highly expressed in adipocytes and elevated levels of FABP-4 are associated with adiposity, female gender, diabetes and hypertension.[26, 55, 56] FABP-4 displays some expression in macrophages and it is thought that FABP-4 increases foam cell formation and induces an inflammatory response.[55, 56]

FABP-4 levels have been associated with LV hypertrophy and systolic and diastolic dysfunction.[55] In patients with chronic heart failure, higher FABP4-levels were independently associated with adverse during follow-up.[26]

In ConHD patients little is known about FABP-4. Recently we observed in a young Fontan cohort a negative association between FABP-4 levels and age at Fontan and peak VO_2 (manuscript accepted). In the current TOF cohort we also observed a negative association between FABP-4 levels and peak VO_2. More research on the role of FABP4 levels in ConHD is required.

Composite endpoint

In this study, as in another recent study from our group, we used a composite endpoint of cardiac death, arrhythmias and a peak VO_2 ≤65% of predicted.[13] Exercise capacity is an established prognostic marker in TOF patients.[11, 30, 31] Clinical guidelines recommend CPET during routine follow-up of TOF patients.[12, 57] Diller *et al*.[30] and Giardini *et al.*[58] observed an association between a lower peak VO_2 and an increased risk of hospitalization and death during follow-up. Likewise in a recent study in a young (25.5 years) TOF cohort, a peak VO_2 ≤65% of predicted was associated with an increased risk for death, sustained ventricular tachycardia and cardiac related hospitalizations.[11] Based on the relations between exercise performance, particularly VO_2 max and subsequent outcome, peak VO_2 ≤65% was included in the composite endpoint used in our study.

Limitations

In our relatively young cohort of TOF patients, the number of hard endpoints was limited. This restriction is a known limitation in research in ConHD patients.[12, 13] We therefore used a composite endpoint of cardiac death, arrhythmias and a diminished exercise tolerance to assess the possible association between biomarkers and cardiac outcome. However, due to the limited number of endpoints it is possible that we have missed associations between biomarkers and endpoints in this study. Detecting biomarker cut-off values for clinical use was not part of the current study and further research is necessary to determine the potential role of the observed biomarkers in clinical practice.

Although the median age of TOF patients in our cohort was quite young, some older patients were part of the analysis. This could have influenced our results.

Late gadolinium enhancement or T1 mapping, useful in detecting local or generalized fibrosis in the myocardium, was not performed in our imaging protocol due to time constraints.[59] Therefore we could not investigate associations between myocardial fibrosis with and potential fibrosis blood biomarkers.

Conclusion

In this study we performed an exploratory analysis of blood biomarkers and their relation to cardiac function and subsequent outcome in a relatively young and contemporary TOF population. We observed that in addition to NT-proBNP, biomarkers such as IGFPB-7, DLK-1, MMP-2 and FABP-4 relate to cardiac function and long-term outcome. These biomarkers may have a role in the clinical follow-up and risk stratification of TOF patients.

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Part III

General Discussion and Summary

Chapter 11

General Discussion

General Discussion

Due to great advances in treatment, the survival rate of patients with severe congenital heart defects (ConHD) such as a Tetralogy of Fallot (TOF) or univentricular hearts have increased dramatically in the last 50 years.[1-3] As a result, the number of adults with ConHD is now larger than the number of children with ConHD.[4]

Patients with univentricular heart defects and patients with TOF are amongst those with the highest risk of complications later on during follow-up. Although many studies have looked at the occurrence-risk of these complications, there remains a clinical need for additional markers to detect early signs of cardiac and circulatory dysfunction. The aim of this thesis was to describe the medium to long-term outcomes of univentricular heart defect patients, treated with the Fontan operation, and repaired TOF patients and to explore clinical parameters, imaging characteristics and laboratory markers which are related to the maintenance of cardiac homeostasis or the development of adverse outcome.

Endpoints in congenital heart disease research

The search for markers with prognostic value in ConHD is ongoing. Several of the established prognostic parameters have mainly been assessed in older ConHD cohorts from earlier surgical eras.[5-7] Therefore the results cannot be simply extrapolated to younger patients operated at a younger age and/or with different treatment strategies. Due to the change in surgical techniques, timing of interventions and improvement of perioperative care the overall survival of ConHD patients has improved.[8-11] It is expected that these improvements in management will influence the morbidity rates at mid- to long-term follow-up.[9, 12-14 15] For these reasons it is important to perform research in younger populations of ConHD patients and to assess their follow-up and determinants of outcome.

Research in ConHD, especially in the contemporary cohorts, is complicated in a way by the successful therapeutic strategies developed in the last decades, resulting in a low incidence of 'hard outcomes' such as cardiac death and documented arrhythmias.[16] This is why additional outcome measurements and composite endpoints often are used. These alternative outcome parameters include cardiac reinterventions and objective clinical parameters such as exercise capacity, imaging parameters and ECG-derived information, e.g. QRS-duration.[17-19]

In this thesis we studied cohorts of contemporary Fontan and repaired TOF patients with a relatively low incidence of hard outcomes. In several chapters (**chapter 3, 4, 5, 7, 8, 9 & 10)** we used a composite endpoint of cardiac death, arrhythmias, cardiac reinterventions, cardiac hospitalization and a cut-off point in exercise capacity, namely a peak oxygen uptake (VO_2) ≤65% of predicted. We used this cut-off point in exercise capacity because a peak VO_2 is a well-known prognostic marker and repeated cardio pulmonary exercise test is recommended by the guidelines.[7, 16, 17, 20, 21] Several studies have established an association between lower peak VO_2 or predicted peak VO_2 and

hospitalization, sustained ventricular tachycardia and death during subsequent follow-up.[7, 17, 22] A recent study in relatively young (25 years) TOF patients observed that a peak VO_2 ≤65% of predicted was related to an increased risk for cardiac hospitalization and death.[17]

Imaging the heart

Cardiac imaging with cardiovascular magnetic resonance imaging (CMR) is an important tool in the follow-up of both Fontan and TOF patients. CMR provides detailed information on anatomy and cardiac and valvular function. In our multicenter prospective COBRA[3] study, TOF and Fontan patients underwent CMR for detailed cardiac assessment. The main advantage of CMR in the follow up of patients with ConHD is that it provides both quantitative information on large vessel and transvalvular flow as well as information on ventricular size and function in geometrically complex ventricles such as the right ventricle (RV) and single ventricle.[23, 24]

In Fontan patients several CMR derived parameters have been associated with clinical outcome.[25] A single ventricle end diastolic volume (EDV) >125 mL/BSA$^{1.3}$ was associated with an increased risk of death of or cardiac transplantation (listing) during 4 year follow-up.[25] In this study by Rathod *et al.*[25] a CMR derived ejection fraction (EF) <40% and a higher cardiac mass were significantly more common in patients who would die or receive a cardiac transplant during the follow-up.[25] In the prospective CMR studies in our Fontan patients (**chapter 4 and 5**) we did not observe an association between CMR derived EDV or EF and subsequent outcome. This might be explained by the younger age of our cohort and the use of other cardiac endpoints. In our study cardiac interventions and arrhythmias were also included in the cardiac endpoint, whereas Rathod *et al.*[25] used endpoints such as death and cardiac transplantation in their analysis. In **chapter 4** we did observe that Fontan patients who would reach an event during subsequent follow-up had a higher cardiac mass.[26] Late gadolinium enhancement (LGE) CMR is a method to assess myocardial fibrosis and has been linked to non-sustained ventricular tachycardia (VT).[27] Recently a diminished CMR-derived global longitudinal strain was found predictive for adverse events including death, cardiac reinterventions, unscheduled hospitalization, heart failure and arrhythmias.[28] In this thesis we did not research LGE CMR or strain analysis.

In TOF patients CMR is the golden standard to monitor pulmonary valve competence and RV and left ventricular (LV) volumes and function.[16, 24, 29] A regular CMR during follow-up is recommended by the guidelines.[16, 24, 29] Serial CMR measurements in TOF patients show progression of RV volumes and pulmonary regurgitation (PR) over time.[30] Progressive RV dysfunction and dilatation are indications for a pulmonary valve replacement (PVR).[29] In addition to the role of CMR in determining the optimal timing for PVR in TOF patients, several CMR parameters have been associated with death, cardiac arrest and major arrhythmias during follow-up.[31, 32] These parameters include conventional ventricular function measurements such as diminished LVEF and RVEF but also reduced RV longitudinal strain and reduced LV circumferential strain measured

by CMR-based feature tracking.[31, 32] Recently Geva *et al.*[33] observed that an increased RV mass volume ratio is associated with death and sustained VT in TOF patients who underwent a PVR and had residual pulmonary stenosis.[33] In our cohort we did not observe an association between RV mass/volume ratio and subsequent outcome (**chapter 9**), which might be explained by the younger age of our patients and limited incidence of outcomes such as VT and cardiac death.

Dobutamine stress CMR

In **chapter 4 and 9** we have focused on the potential prognostic value of a dobutamine stress CMR in Fontan and TOF patients. In **chapter 4** we observed that in a young Fontan cohort the ventricular response to dobutamine stress was predictive for adverse events during follow-up. Fontan patients with a diminished functional reserve (FR) (EF_{stress}-EF_{rest}) experienced a worse event-free survival.[26] Similarly to Fontan patients, in TOF patients we observed in **chapter 9** an association between the ventricular response to dobutamine stress CMR and outcome. An abnormal stress response (e.g. inability to increase EF or decrease end systolic volume (ESV)) was associated with an increased risk of the composite endpoint during 8 year follow-up, as was the relative change in RVESV during stress.

In ConHD patients an association between the response to dobutamine stress and adverse outcome previously has only been described in patients with a systemic RV in a biventricular circulation.[34] In these patients an abnormal stress response was predictive for adverse outcome during 8 years of follow-up.[34] In TOF patients a smaller relative increase in RVEF during stress has been associated with a large decrease in peak VO_2 during subsequent five year follow-up.[35] To our knowledge we are the first to describe an association between the ventricular response to dobutamine stress and adverse events in Fontan and TOF patients. Both patients groups were asymptomatic at the time of dobutamine CMR and none of the other size and function imaging parameters we tested for this purpose were associated with outcomes. Our findings therefore highlight the potential importance of using stress imaging techniques to detect sub-clinical ventricular dysfunction in ConHD patients.

Blood biomarkers

In **chapter 5 and 10** we have described an exploratory approach to assess blood biomarkers involved in maintaining cardiac function and outcome in Fontan and TOF patients. Blood biomarkers could represent pathways that are involved in maintaining cardiac function and the development of heart failure.

Relatively little is known about het processes leading to myocardial changes to adapt to chronic abnormal loading conditions in ConHD.[36, 37] It is thought that processes involving inflammation and cardiac fibrosis are essential in the deterioration of cardiac function.[36] Furthermore, pathways and biomarkers involved in heart failure may be different in ConHD children compared to adults with heart failure, including adults with ConHD.[36, 38, 39] In the COBRA[3] project, which forms the backbone of this thesis, we have focused on the following blood markers:

NT-proBNP

In the last decades neurohormones such as brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) have received much attention as a marker for cardiac disease.[40] The ventricular myocyte releases NT-proBNP as a response to stretch and in acquired heart failure patients NT-proBNP levels have an important role the clinical follow-up.[41, 42]

In TOF and Fontan patients (NT-pro)BNP levels are related to the clinical condition.[43-46] Although NT-proBNP levels are often within normal range in Fontan patients,[47] Fontan patients with heart failure, patients in which older Fontan techniques were used and in patients with a morphological RV higher NT-proBNP levels are found.[43, 48-50] Other studies observed correlations between (NT-pro)BNP levels and exercise capacity, EDV, cardiac mass or atrioventricular valve regurgitation in Fontan patients.[40, 45, 51] In **chapter 5** we described that elevated NT-proBNP levels were associated with adverse outcome, indicating its potential value in the routine follow-up in young and contemporary Fontan patients. In recent international guidelines the monitoring of (NT-pro)BNP levels in Fontan patients is not mentioned.[16, 21] Our results indicate the value of NT-proBNP levels in the follow-up of young Fontan patients.[47]

In TOF patients numerous studies have shown correlations between NT-proBNP and impaired LV function, degree of pulmonary regurgitation, RVEDV size and exercise capacity.[40, 44, 52-55] Elevated NT-proBNP, unadjusted for age, has also been associated with adverse clinical outcome in adult TOF patients.[44, 52] In **chapter 9 and 10** we prospectively evaluated the value of NT-proBNP in relatively young TOF patients. Similar to other studies[44, 52] we observed that NT-proBNP levels were associated with adverse events during follow-up. However, in our analysis in **chapter 10**, NT-proBNP lost its predictive value when adjusted for age. Our results in combination with the existing literature indicate that NT-proBNP may have a role in monitoring of cardiac function and deterioration in TOF patients.[40, 56] However the exact prognostic value of NT-proBNP still needs to be determined.[56]

Inflammatory markers

Inflammation and a pro-inflammatory state have been associated with heart failure in patients with acquired heart disease.[57-59] Besides the role of the inflammatory pathways in chronic heart failure, inflammation is an important factor in the remodeling process after myocardial infarction.[57, 59] In this thesis we examined blood biomarkers which represent an inflammatory response and their potential role in ConHD. Suppression of tumorigenicity 2 (ST2) is a marker for inflammation and remodeling, fibrosis and apoptosis in the myocardium and is upregulated in response to myocardial stress.[60-62] Fatty acid-binding protein 4 (FABP-4) expression plays a role in the activation of several inflammatory pathways in adipocytes and macrophages and is associated with diabetes, atherosclerosis and metabolic syndrome.[63-65] Cardiomyocytes also produce FABP-4, in mice overexpression of FABP-4 by the cardiomyocyte is associated with pressure induced cardiac hypertrophy.[64]

In humans FABP-4 has mainly been studied in acquired heart disease and elevated FAPB-4 levels have been associated with adverse outcome and lower peak VO_2.[63 66] In **chapter 5 and 10**, we observed an association between higher FABP-4 levels and diminished peak VO_2 in both the Fontan and TOF patients. FABP-4 may therefore have a potential role in the follow-up in ConHD patients, however more studies have to be performed to assess its prognostic value. ST2 has been studied in cohorts of ConHD patients and has been associated with all-cause mortality in large adult ConHD cohorts.[60, 62] In **chapter 5** we observed that in young Fontan patients higher ST2 levels at baseline were associated with severe events during follow-up. We did not observe an association between ST2 levels and adverse outcome in our TOF patients.

Fibrosis markers

Myocardial fibrosis is relatively common in Fontan and TOF patients and has been associated with morbidity.[27, 67-69] Disturbances in the equilibrium between the production of collagen by fibroblasts and the degradation of the extracellular matrix can result in myocardial fibrosis.[68] The mechanisms of developing myocardial fibrosis can be acute (due to an operation e. g. cardiac injury) or chronic (caused by abnormal hemodynamics) in origin.[67] In ConHD patients both mechanisms are likely to be important. Myocardial fibrosis has been linked to ventricular arrhythmias and cardiac death and assessing myocardial fibrosis through non-invasive imaging and/or blood biomarkers could help with risk stratification in the individual patient.[27, 67-69] In **chapter 5 and 10** we discuss several potential blood biomarkers that have been linked to collagen deposition and fibrosis.

Insulin-like growth factor-binding protein 7 (IGFBP-7) has been linked to collagen deposition. We observed that IGFBP-7 was associated with adverse outcome in TOF patients. In our Fontan patients we observed an association between increased levels of IGFBP-7 and diminished peak VO_2. Another promising biomarker linked to collagen deposition is DLK-1. In mouse models, DLK-1 knock-out mice have increased collagen deposition in the myocardium.[70] In our Fontan patients we observed that patients with lower levels of DLK-1 display a better severe event-free survival and a higher FR.

Imaging techniques, particularly CMR, can be used to characterize fibrosis in the myocardium. CMR provides this opportunity using LGE and/or T1 mapping.[71-73] Because of limitations in scanning time we did not use these techniques in our studies. Therefore we could not confirm the association of both IGFBP-7 and DLK-1 and actual fibrosis in the myocardium. This could be the subject of further research.

Outcomes after the Fontan operation

In **chapter 2** we reviewed the medium to long term outcomes and the current 'state of the art' Fontan strategy. There are several preoperative factors that have been identified to have impact on mortality and prognosis. These factors include male gender, hypoplastic left heart syndrome (HLHS), atrioventricular (AV) valve regurgitation, heterotaxy syndrome and elevated pulmonary artery pressure.[74-76] In addition,

postoperatively higher EDV, worse peak VO_2 and diminished global longitudinal strain have been associated with adverse outcome.[7, 25, 74, 75, 77-79] Also the choice of surgical technique has potential implications for the long-term outcomes of patients.

Intra-atrial lateral tunnel or extra cardiac conduit

The two surgical total cavopulmonary connection (TCPC) techniques currently in use are the intra-atrial lateral tunnel (ILT) and the extra cardiac conduit (ECC) technique.[76] In **chapter 3** we retrospectively studied the long-term outcomes of these two TCPC techniques. Although the long-term outcomes after TCPC have been studied extensively, a shift in surgical preference from the ILT to the ECC technique in many centers complicates the comparison.[80] In our multicentre study one centre continued to use the ILT technique, giving us the opportunity to compare a population of ILT and ECC patients from the same surgical era with a comparable follow-up duration.

We observed late survival rates of 94% at 10-year and 92% at 15 years after TCPC, without differences in late survival between the two TCPC techniques. Patients with an ILT experienced a worse arrhythmia free survival, which has also been observed in other studies.[80, 81] ECC patients received significantly more catheter and surgical based reinterventions, mainly due to replacements of 16-mm conduits.[82] However, over time small alterations were made in the ILT and ECC technique. The atrial baffle ILT evolved into the prosthetic ILT and 16 mm conduits were no longer used for the ECC.[83, 84] We compared the long-term results of these newer ILT and ECC techniques and observed no differences in long-term arrhythmia-free and reintervention-free survival.[12]

In theory there are several potential differences between the ILT and ECC technique. ECC patients seem more prone to develop thromboembolic events, while ILT patients seem more at risk for arrhythmias.[80, 81, 85] Another potential benefit of the ECC is the option to perform the TCPC completion with shorter CPB times, or even off-pump.[81, 86-88] This could potentially impact ventricular function during long term follow-up. In previous studies several small differences in clinical parameters have been observed between ILT and ECC patients.[45, 89] Assessed by echocardiography ECC patients had poorer diastolic function, lower TDI-based TEI-index and a shorter isovolumic relaxation time.[45] Assessed by CMR, ECC patients had a significantly higher EF at rest, although this was not observed in a larger cohort.[45, 89] During dobutamine stress ECC patients were able to increase ventricular stroke volume in contrast to ILT patients. Also cardiac index en EF during stress were higher and afterload was significantly lower in ECC patients.[45] Some studies have found less favourable peak oxygen uptake in ILT patients.[90, 91]

Taken together our observations and the results of other studies do not suggest a clear benefit for one of the two techniques. The choice of TCPC technique to be used depends on local surgical prevalence.

Fontan failure

In patients with ConHD the incidence of heart failure is 1.2 per 1000 patients-years.[92]

Hospitalization for heart failure has a worse prognosis with a reported 1 year mortality of 24%.[92] The Fontan circulation creates a situation with elevated systemic venous pressure and decreased systemic output.[3, 76] Impairments in the Fontan circulation can be localized in the systemic venous system, the Fontan pathway, the pulmonary vascular system, the single ventricle and the aorta.[76] Like in other ConHD patients, the incidence of heart failure in Fontan patients increases with age.[92] Patients operated on with more contemporary Fontan techniques experience lower heart failure rates compared the older Fontan technique patients, although this comparison is in part hampered by differences in duration of follow-up.[76, 93]

The treatment of heart failure in Fontan patients is based on improving myocardial function and relieving and treating possible underlying causes of heart failure.[94] A heart transplantation is the last available option and the use of cardiac transplantation in Fontan patients varies across centers worldwide.[8, 9, 76] After transplantation 5 year survival ranges from 60% to 67% and is less in Fontan patients compared to other ConHD.[95-97]

Early recognition of patients at risk for adverse events and Fontan failure is necessary. In this thesis we have explored several of these potential markers such as dobutamine stress CMR and biomarkers. See previous parts of this chapter.

Outcomes after Tetralogy of Fallot repair

We reviewed the outcomes and treatment of TOF in **chapter 6**. After TOF-repair overall survival has significantly improved over the last decades, mainly due to the decrease in early mortality.[11, 14, 98, 99] Morbidity, often related to pulmonary regurgitation (PR) is common after TOF-repair. PR leads to a volume overloaded RV which in turn can lead to RV dilatation, ventricular dysfunction and arrhythmias.[6, 14, 100, 101]

Pulmonary valve replacement

To restore the function of the pulmonary valve TOF patients often undergo a PVR. In **chapter 8** we observed a PVR-free survival of 96% at 10-year, 83% at 20-year and 48% at 30 year after TOF-repair. Patients with a transannular patch (TP) or a staged TOF-repair receive more frequently a PVR.[13, 14, 102, 103] It is thought that if a PVR is performed on time the volumes and function of the RV normalize and improve also the functional status of the patient.[16, 101, 104-106] A homograft or a bio prosthetic valve are the most commonly used valves. However these valves have a limited lifespan.[107]

Indications for performing PVR have been given in guidelines and are based on the presence of symptoms, degree of PR, RVEDV, RVESV and exercise capacity.[16, 21] However, survival benefit of PVR using the current criteria has not yet been demonstrated.[16, 101, 104, 105]

Transatrial transpulmonary TOF-repair

The surgical approach of TOF-repair has changed considerably over time. In the initial years of surgery for TOF, repair consisted of a large RV incision and a TP across the RV outflow tract (RVOT). This technique later evolved into the primary transatrial

transpulmonary approach which reduced the use of a TP and ventriculotomy.[1, 14, 100, 103] The transatrial transpulmonary approach thereby potentially reduces myocardial scaring and residual PR.[14, 100] In **chapter 7 and chapter 8** we describe the long-term follow-up of a retrospective cohort of 453 TOF patients operated on with the transatrial transpulmonary technique. We observed an overall survival of 96% at 20 years and 93% at 30 years after TOF-repair. Studies describing the long-term follow-up of contemporary surgical TOF-repair are relatively scarce and reported 25-year overall survival has ranged between 93-97%.[98, 99] In our study the event-free survival was 62% at 20 years and 34% at 30 years and was worse for TP patients. Park *et al.*[99] reported a 46.6% 20-year freedom from reinterventions and reoperations. This is lower than in our cohort, which is most likely explained by the presence of both transventricular and trans-atrial repaired TOF patients in their cohort. In a sole trans-atrial cohort, D'udekem *et al.*[98] observed a 75% 25-year freedom of reoperations, they did not report data on other reinterventions or events.

After TOF repair the incidence of supraventricular tachycardia (SVT) increases with increasing follow-up duration.[108, 109] In adult TOF patients the incidence of arrhythmias is quite high. In a cohort of patients median 35 years after TOF repair 22% had experienced SVT and 9% experienced ventricular tachycardia.[109] In another large cohort of older TOF patients (mean age 36.8 years), 43.3% of the patients had a sustained arrhythmia or had received an intervention for arrhythmias.[108] In these older TOF patients reported risk-factors for arrhythmias are older age at TOF-correction, longer QRS duration and an extended ventriculotomy.[17] It seems that TOF patients operated on in the current era with more contemporary and valve sparing techniques display a lower risk of arrhythmias during follow-up.[110]

Timing of TOF-repair

Besides the changes in surgical techniques over time, the age at which the TOF-repair is performed have changed in the last decades.[14, 99, 103, 111] In **chapter 7** we show a decrease in median age from 1.17 years in the patients operated on between 1970-1980 to 0.33 years in the patients operated on between 2000-2012.[14] Nowadays there is no agreement on the optimal timing of primary TOF repair.[14, 111-113] Some centers advocate early TOF-repair because it minimizes the time at risk for hypoxia, cyanotic spells and RV pressure overload.[112, 114] However there are disadvantages of early repair, including a longer intensive care unit stay and a higher prevalence of TP's and reinterventions.[98, 102, 113, 115, 116] In **chapter 8** we performed a multicenter retrospective analyses in patients who underwent elective primary TOF-repair. We observed that patients who underwent elective TOF-repair before the age of 6 months received more TP's and experienced a significantly worse event-free survival compared to the patients operated on after 6 months of age.

Conclusions

In this thesis we assessed clinical parameters, imaging characteristics and laboratory markers and their relationship to clinical outcome in TOF and Fontan patients.

We observed a relatively good long-term survivals after contemporary TCPC completion and TOF-repair. However the morbidity remains relatively high. We observed that events after TOF repair were more prevalent in TOF patient who underwent elective primary TOF-repair before 6 months of age compared to those who were older than 6 months of age. In Fontan patients, similar long-term survival rates were observed after staged ILT and ECC. However, late after staged TCPC arrhythmias were more prevalent in ILT patients and re-interventions were more prevalent in ECC patients. These differences in events during follow-up disappeared in patients operated on with more contemporary TCPC techniques.

Using dobutamine stress CMR we found that the ventricular reserve as tested with this method related to adverse events during long-term follow-up of both TOF and Fontan patients. Furthermore, in our relatively young patient groups, the response to stress CMR was a better predictor for later adverse events than previously reported risk factors. This suggest this response might be a marker for early dysfunction and therefore could be an additional tool in the risk stratification of young TOF and Fontan patients. Next to imaging parameters we also explored several blood biomarkers in our prospective studies. Adverse events in Fontan patients were associated with elevated NT-proBNP and ST2 levels and lower DLK-1 levels. In TOF patients we observed an association between elevated IGFBP-7 levels and adverse outcome. In both Fontan and TOF patients we observed that higher DLK-1 levels, a marker potentially involved in fibrosis pathways, were associated with a favorable ventricular response to dobutamine stress CMR. In Fontan patients higher DLK-1 levels were associated with a better severe event-free survival.

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Chapter 12

Summary

Samenvatting

SUMMARY

In **chapter 1**, the introduction of this thesis, we provide an overview of the prevalence of congenital heart disease (ConHD) and specifically of univentricular heart defects and Tetralogy of Fallot (TOF). We discuss commonly used modalities to assess clinical condition in ConHD patients, such as echocardiography, cardiovascular magnetic resonance imaging (CMR), cardiopulmonary exercise test (CPET) and blood marker assessment. Furthermore this chapter describes the aims and outline of this thesis.

Part I: Fontan circulation

In **chapter 2** we investigate the current literature on univentricular heart defects. We discuss the state of the art Fontan strategy, common complications and interventions after the Fontan operations and factors associated with long-term survival and morbidity. We also discuss the remaining challenges we face in the Fontan field.

In **chapter 3** we investigate the serial follow-up and the long-term outcomes after the staged total cavopulmonary connection (TCPC). We compare the two TCPC techniques, the intra-atrial lateral tunnel and the extracardiac conduit (ECC). In this study we include 208 TCPC patients (103 ILT, 105 ECC) with a median follow-up duration of 13.2 years after TCPC. After 15 years of follow-up the overall survival was comparable; 81% for ILT and 89% for ECC. Patients with an ILT experience more often arrhythmias during follow-up, patients with an ECC experience more surgical and catheter-based reinterventions. Over time the ILT and ECC modifications changed and in the patients operated on with these current modifications we did not observe a significant difference in arrhythmias-free survival and reintervention-free survival during follow-up.

In **chapter 4** we research the additional value of a dobutamine stress CMR in contemporary Fontan patients. In prospective studies 92 patients receive a dobutamine stress CMR at a median age of 11.5 (9.8 – 15.3) years. After a median follow-up of 5.8 (4.9 – 10.0) years 23 patients (25%) developed a cardiac event. Patients who develop an event have a significantly lower functional reserve (Ejection Fraction $(EF)_{stress} - EF_{rest}$) compared to the patients who did not develop an event. Likewise the event-free survival was better for the patients with the highest functional reserve.

In **chapter 5** we study 133 Fontan patients who receive a dobutamine stress CMR, a cardiopulmonary exercise test (CPET) and blood sampling. The median age at time of study was 13.2 (10.4 – 15.9) years. After a median follow-up of 6.2 (4.9 – 6.9) years, 36 (27.1%) patients experienced an event of whom 13 (9.8%) had a severe event. We observe that elevated levels of NT-proBNP, GDF-15 and vWF are associated with worse outcome during follow-up. Elevated levels of DLK-1 correlate with a higher functional

reserve during dobutamine stress CMR (a good prognostic sign, see chapter 4). Similary, patients with higher DLK-1 levels experience less severe events during follow-up.

Part II: Tetralogy of Fallot

In **chapter 6** we research the literature on TOF and we describe the currently used treatment strategy. We elaborate on the long-term survival and residual problems such as pulmonary regurgitation, remaining right ventricle (RV) obstruction, RV dysfunction and arrhythmias. Important imaging modalities in TOF patients such as CMR and echocardiography are also discussed as are the remaining challenges in TOF.

In **chapter 7** we investigate the long-term outcomes in 453 TOF patients corrected with the transatrial-transpulmonary approach. A transannular patch (TP) was used in 65% of the patients. We observe a good long-term survival with an early mortality of 1.1% and a 25-year survival of 92%. No differences in overall survival between patients with and without a TP were observed. A pulmonary valve replacement was common during follow-up and occurred more frequent in the TP-group. The use of a TP was a predictor for poorer outcome after TOF repair.

In **chapter 8** we investigate the same cohort as described in **chapter 7** with an additional 5 years of follow-up. We investigate the serial follow-up long-term after transatrial-transpulmonary TOF-repair. The overall survival was 96% at 20 years and 93% at 30 years after TOF-repair. Morbidity however was common, the event-free survival was 62% at 20 years and 34% at 30 years after TOF-repair. In this chapter we also describe the influence of the timing of the elective primary TOF-repair on long-term outcome. Patients who underwent elective early repair (<6 months) experienced more events during follow-up.

In **chapter 9** we investigate the additional value of a dobutamine stress CMR in TOF patients. In previous prospective multicenter studies 100 patients receive a low-dose dobutamine stress CMR. The median age at time of study was 7.8 years (13.5 – 34.0) years. After a median follow-up of 8.6 (6.7 – 14.1) years 10 patients reached the composite endpoint. An abnormal stress response (inability to increase EF or decrease end systolic volume (ESV)) was more frequently observed in the patients who reached the composite endpoint (30% vs 4.4%). The ventricular response to dobutamine stress predicted clinical outcome in these TOF patients.

In **chapter 10** we assess blood biomarkers in a relatively young TOF cohort with a median age of 19.2 (14.6–25.7) years. A total of 137 patients receive a dobutamine stress CMR, blood sampling and a CPET. After a median follow-up of 8.7 (6.3–10.7) years, (14.6%) 20 patients reached the composite endpoint. We observe that elevated

levels of IGFBP-7 and MMP-2 were associated were associated with adverse outcome during follow-up. Similar to in Fontan patients, we observe that higher levels of DLK-1 were associated with a good response to a dobutamine stress CMR.

Part III: General Discussion

In **chapter 11** we discuss all the studies in this thesis and the context of our findings. We observe a relatively good long-term survival in our TOF and Fontan patients, however the long-term morbidity remains high. In this thesis we assess several clinical parameters, imaging characteristics and blood biomarkers and their relationship to clinical outcome in TOF and Fontan patients. These parameters can help in the risk-stratification of our TOF and Fontan patients.

SAMENVATTING

In **hoofdstuk 1**, de introductie van dit proefschrift, geven we een overzicht van de prevalentie van congenitale hartziekte (ConHD) en specifiek van univentriculaire hartafwijkingen en Tetralogy of Fallot (TOF). We bespreken veelgebruikte technieken om de klinische toestand bij ConHD patiënten te beoordelen, zoals echocardiografie, cardiovasculaire MRI (CMR), cardiopulmonale inspanningstest (CPET) en bloed biomarkers. In dit hoofdstuk worden ook de doelen van dit proefschrift beschreven.

Deel I: Fontan circulatie

In **hoofdstuk 2** onderzoeken we de huidige literatuur over univentriculaire hartafwijkingen. We bespreken de huidige Fontan-strategie, veel voorkomende complicaties en interventies na de Fontan-operaties en factoren die samenhangen met overleving en morbiditeit op de lange termijn. We bespreken ook de resterende uitdagingen waarmee we worden geconfronteerd op het gebied van de Fontan circulatie.

In **hoofdstuk 3** onderzoeken we de seriële follow-up en de lange termijn resultaten na de gestageerde totale cavopulmonale connectie (TCPC). We vergelijken de twee TCPC technieken, de intra-atriale laterale tunnel (ILT) en de extracardiac conduit (ECC). In deze studie beschrijven we 208 TCPC-patiënten (103 ILT en 105 ECC) met een mediane follow-up duur na TCPC van 13.2 jaar. Na 15 jaar volgen van deze patiënten (follow-up) was de totale overleving vergelijkbaar tussen de twee technieken. Patiënten met een ILT kregen vaker een aritmie tijdens de follow-up, patiënten met een ECC ondergingen meer reïnterventies zoals hartkatheterisaties en hartoperaties. Gedurende de jaren veranderden de ILT- en ECC-techniek. In de patiënten die met deze huidige modificaties werden geopereerd zagen we geen verschil in aritmie-vrije overleving en reïnterventie-vrije overleving gedurende de follow-up.

In **hoofdstuk 4** onderzoeken we de toegevoegde waarde van een dobutamine stress CMR in jonge Fontan patiënten. 92 patiënten krijgen een dobutamine CMR, de mediane leeftijd van de patiënten was 11.5 jaar ten tijde van de CMR. Na een gemiddelde follow-up van 5.8 jaar ontwikkelden 23 patiënten (25%) een cardiaal event. Patiënten die tijdens de follow-up een cardiaal event ontwikkelen hebben een significant lagere functionele reserve (ejectie fractie $(EF)_{stress} - EF_{rest}$) in vergelijking met de patiënten die geen cardiaal event ontwikkelen gedurende de follow-up.

In **hoofdstuk 5** onderzoeken we 133 Fontan-patiënten die een dobutamine stress CMR, een CPET en bloedafname krijgen. De mediane leeftijd ten tijde van het onderzoek is 13.2 jaar. Na een follow-up van 6.2 jaar hebben 36 (27.1%) patiënten een cardiaal

event ontwikkeld waarvan 13 (9.8%) een ernstig cardiaal event. We zien dat verhoogde levels van NT-proBNP, GDF-15 en vWF geassocieerd zijn met een slechtere uitkomst gedurende de follow-up. Verhoogde levels van DLK-1 zijn ook geassocieerd met een betere functionele reserve tijdens de dobutamine CMR (een goed prognostisch teken, zie hoofdstuk 4). Ook hebben patiënten met hogere DLK-1 levels minder ernstige cardiale events gedurende de follow-up.

Deel II: Tetralogie van Fallot

In **hoofdstuk 6** onderzoeken we de literatuur over en beschrijven we de huidige behandelingsstrategie bij patiënten met een TOF. We bespreken de lange termijn overleving en resterende morbiditeit zoals pulmonaal insufficiëntie, resterende rechter ventrikel (RV) obstructie, RV-dysfunctie en ritme problemen. Belangrijke beeldvormingsonderzoeken bij TOF-patiënten zoals CMR en echocardiografie worden ook besproken, evenals de resterende uitdagingen bij TOF patiënten.

In **hoofdstuk 7** beschrijven we de lange termijn uitkomsten van 3 TOF patiënten die een transatriale transpulmonale TOF operatie krijgen. Een transannulaire patch (TP) wordt gebruikt in 65% van de patiënten. We observeren een relatief goede lange termijn overleving met een vroege mortaliteit van 1.1% en een 25-jaars overleving van 92%. We zien geen significant verschil in overleving tussen de patiënten met en zonder een TP. Relatief veel patiënten krijgen een pulmonaalklep vervanging gedurende de follow-up, dit komt vaker voor in de TP-groep. Het gebruik van een TP is een voorspeller voor slechtere uitkomsten na de TOF operatie.

In **hoofdstuk 8** onderzoeken we hetzelfde cohort als in **hoofdstuk 7** alleen met 5 jaar extra follow-up. We beschrijven de seriële follow-up van deze patiënten op lange termijn na de transatriale-transpulmonale TOF operatie. De totale overleving is relatief goed: 96% overleving na 20 jaar en 93% overleving 30 jaar na de TOF operatie. Echter een relatief lage mortaliteit staat niet gelijk aan een lage morbiditeit, de event-vrije overleving is 62% na 20 jaar en 34% 30 jaar na de TOF operatie. Daarnaast onderzoeken we de invloed van de timing van een electieve TOF operatie op de lange termijn uitkomsten. Patiënten die een electieve vroege TOF operatie kregen (<6 maanden) ontwikkelen meer cardiale events gedurende de follow-up.

In **hoofdstuk 9** onderzoeken we in TOF patiënten de toegevoegde waarde van een dobutamine CMR. In eerdere studies krijgen 100 TOF patiënten een dobutamine stress CMR. De mediane leeftijd ten tijde van het onderzoek is 7.8 jaar en na een gemiddelde follow-up van 8.6 jaar bereiken 10 patiënten een klinisch eindpunt. Een abnormale ventriculaire stress reactie (het onvermogen om EF te verhogen of eind systolisch volume (ESV) te verlagen) wordt vaker waargenomen bij de patiënten die het klinische

eindpunt bereiken (30% versus 4.4%). De ventriculaire respons op dobutamine stress lijkt klinische uitkomsten te voorspellen bij deze TOF patiënten.

In **hoofdstuk 10** onderzoeken we 137 relatief jonge TOF patiënten die een bloedafname, CPET en stress CMR krijgen. Na een mediane follow-up van 8.7 jaar bereiken (14.6%) 20 patiënten het klinische eindpunt. We zien dat hogere levels van IGFBP-7 en MMP-2 zijn geassocieerd met een slechtere uitkomst tijdens de follow-up, gecorrigeerd voor de leeftijd op het moment van de bloedafname. Net als bij de Fontan patiënten zien we dat hogere niveaus van DLK-1 geassocieerd zijn met een betere ventriculaire reactie op dobutamine stress.

Deel III: Algemene discussie

In **hoofdstuk 11** bespreken we alle studies in dit proefschrift en de bredere context van onze bevindingen. We zien een relatief goede overleving in onze Fontan en TOF patiënten, echter de morbiditeit blijft hoog. In dit proefschrift onderzoeken we de relatie tussen klinische parameters, beeldvormingsonderzoeken en bloed uitslagen met de klinische uitkomsten in TOF en Fontan patiënten. Deze bevindingen kunnen helpen in de klinische zorg van TOF en Fontan patiënten.

Part IV

Appendices

LIST OF ABBREVIATIONS

AOV	aortic valve
APC	atrio-pulmonary connection
APVS	absent pulmonary valve syndrome
ASD	atrial septal defect
AV	atrio ventricular
AVSD	atrioventricular septal defect
AVV	atrioventricular valve
BDG	bidirectional Glenn anastomosis
BMI	body mass index
BNP	brain natriuretic peptide
BSA	body surface area
BT	Blalock-Taussig
CCS	Canadian cardiovascular society
CHD	congenital heart defect
CI	confidence interval
CMR	cardio magnetic resonance imaging
CoA	aortic coarctation
COBRA^3	Congenital heart defects: Bridging the gap between Growth, Maturation, Regeneration, Adaptation, late Attrition and Ageing
ConHD	congenital heart defect
CPB	cardiopulmonary bypass
CPET	cardiopulmonary exercise test
DA	ductus arteriosus
DILV	double inlet left ventricle
DLK-1	protein delta homolog 1
DORV	double outlet right ventricle
ECC	extra-cardiac conduit
EDV	end diastolic volume
EDFF	end-diastolic forward flow
EF	ejection fraction
EMC	Erasmus medical centre
ESV	end systolic volume
FABP-4	fatty acid binding protein 4
FR	functional reserve
Gal-3	galectin-3
GDF-15	growth differentiation factor 15
HLHS	hypoplastic left heart syndrome
HR	hazard ratio
ICD	implantable cardioverter-defibrillator
ICU	intensive care unit

IGFBPs	insulin-like growth factor binding proteins
IGFBP-1	insulin-like growth factor binding protein 1
IGFBP-7	insulin-like growth factor binding protein 7
ILT	intra-atrial lateral tunnel
IQR	interquartile range
LGE	late gadolinium enhancement
LPA	left pulmonary artery
LV	left ventricle
LVEDV	left ventricular end diastolic volume
LVEF	left ventricular ejection fraction
LVESV	left ventricular end systolic volume
LVSV	left ventricular stroke volume
mBT	modified Blalock-Taussig
MMP-2	matrix metalloproteinase
MRI	magnetic resonance imaging
NOACs	Novel oral anticoagulants
NPX	normalized protein expression
NT-proBNP	N-terminal prohormone brain natriuretic peptide
NYHA	New York Heart Association Classification
OHCA	out of hospital cardiac arrest
PA	pulmonary artery
PCPC	partial cavo-pulmonary connection
PDA	persistant ductus arteriosus
PEA	proximity extension assay
PLE	protein-losing enteropathy
PM	pacemaker
PR	pulmonary regurgitation
PS	pulmonary stenosis
PVR	pulmonary vascular resistance
PVR	pulmonary valve replacement
RPA	right pulmonary artery
RER	respiratory exchange ratio
RUMC	Radboud university medical centre Nijmegen
RV	right ventricle
RVEDV	right ventricular end diastolic volume
RVEF	right ventricular ejection fraction
RVESV	right ventricular end systolic volume
RVOT	right ventricular outflow tract
RVOT	right ventricular outflow tract obstruction
RVSV	right ventricular stroke volume
SD	standard deviation
sST2	soluble form of suppression of tumorigenicity 2

ST2	suppression of tumorigenicity 2
STE	speckle tracking echocardiography
SV	single ventricle
SV	stroke volume
SVT	supraventricular tachycardia
TAP	transannular patch
TCPC	total cavo-pulmonary connections
TE	thromboembolism
TEs	thromboembolic events
TGFβ	transforming growth factor beta
TOF	Tetralogy of Fallot
TOFr	Tetralogy of Fallot repair
TP	transannular patch
TR	tricuspid regurgitation
VA	ventriculo-arterial
VACTERL	vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula and/or esophageal atresia, renal & radial anomalies and limb defects
VCO_2	carbon dioxide production
VKA	vitamin K antagonists
VO_2	oxygen uptake
VSD	ventricular septal defect
VT	ventricular tachycardia
vWF	von Willebrand Factor
4D	four dimensinoal

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Courses	**Year**
Patient oriented research course (CPO)	2015
Basic introduction SPSS (MolMed)	2015
Congenital heart Disease course (Coeur)	2015
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Open Clinica course	2016
Heart failure research course (Coeur)	2016
Right Ventricle failure symposium (Coeur)	2016
Hands on Course on pediatric CMR (Society of Pediatric Radiology)	2016
Survival analysis course (MolMed)	2016
Basic imaging course, part I (Coeur)	2017
Basic statistical Methods (CCO2a) (NIHES)	2017
Advance Imaging course, part II (Coeur)	2017
Imaging and diagnostics course, part III (Coeur)	2017
Integrity in Science for PhD students	2017
Sex and gender in cardiovascular research (Coeur)	2017
Congenital heart disease (Coeur)	2018
Biomedical English Writing and Communication	2018
Heart transplantation and organ transplantation course (Coeur)	2019
Research meetings Pediatric Cardiology Department	2015-2019

Conferences and presentations	
Hartvrienden Hartstichting, Utrecht *(presentation)*	2015
SPR 12th Advanced Symposium on Cardiovascular Imaging, Houston, United States	2016
Hartekind dag UMCN, Nijmegen *(presentation)*	2016
Sophia Research day, Rotterdam *(presentation)*	2017
EuroCMR 2017, Prague, Czech Republic *(2 presentations)*	2017
WCPCCS 2017, Barcelona, Spain *(2 poster presentations)*	2017

CHOP Cardiology 2018, Fontan Symposium, Arizona, United states *(2 oral presentations)*	2018
Sophia Research day, Rotterdam *(presentation)*	2018
Amalia Research day, Nijmegen *(2 presentations)*	2018
AEPC 2018, Athens, Greece *(presentation)*	2018
Cardiovascular Development meeting, Marseille, France	2018
Cobra Masterclass, Utrecht *(presentation)*	2019
AEPC 2019, Seville, Spain *(poster presentation)*	2019

Teaching

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Supervising Master thesis: Cardiac T1 mapping in congenital heart diseases	2018

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CURRICULUM VITAE

Eva van den Bosch was born on the 5th of June 1991 in Culemborg, the Netherlands. She completed her secondary education at the Guido de Brès in Amersfoort in 2008. Eva started her medical training in 2008 at the Erasmus University of Rotterdam. During her minor 'congenital heart defects' she became interested in congenital and pediatric cardiology. Later she did a clinical intership at the Departent of Pediatric Cardiology (Erasmus Medical Center, Rotterdam) as wel as a research internship at the Department of Pediatric Cardiology (Radboud University Medical Center, Nijmegen & Erasmus Medical Center, Rotterdam). Eva obtained her medical degree in February 2015, thereafter she started as a PhD Candidate Pediatric Cardiology in the multicenter COBRA^3 study. Her study mainly focused on the long-term outcomes of patiënts with a Tetralogy of Fallot or Fontan circulation. She was supervised by Prof. Dr. W.A. Helbing (Department of Pediatric Cardiology, Erasmus Medical Center, Rotterdam), Prof. Dr. N.A Blom (Department of Pediatric Cardiology, Leiden University Medical Center) and Dr. L.P. Koopman (Department of Pediatric Cardiology, Erasmus Medical Center, Rotterdam). From May 2020 onwards she is working as a resident (ANIOS) at the Department of Cardiology at the Canisius Wilhelmina Ziekenhuis in Nijmegen.

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