Technische Universität München

Fakultät für Medizin

Risk Factors for Failure to Successful Fontan Completion Following the Bidirectional Cavopulmonary Shunt

Lisa Marie Anderl

Vollständiger Abdruck der von der Fakultät für Medizin
der Technischen Universität München zur Erlangung einer

Doktorin der Medizin

genehmigten Dissertation.

Vorsitzender:

Prof. Dr. Florian Eyer

Prüfer der Dissertation:

1. Prof. Dr. Jürgen Hörer

2. apl. Prof. Dr. Walter Eichinger

Die Dissertation wurde am 16.01.2023 bei der Technischen Universität München eingereicht und durch die Fakultät für Medizin am 18.07.2023 angenommen.

dedicated to my grandparents

Table of Contents

Abbreviations

AA	aortic atresia
ASD	atrial septal defect
ASE	atrioseptectomy
AVSD	atrioventricular septal defect
AVV	atrioventricular valve
AVVR	atrioventricular valve regurgitation
BCPS	bidirectional cavopulmonary shunt
CHD	congenital heart defect
CPB	cardiopulmonary bypass
DILV	double inlet left ventricle
DIRV	double inlet right ventricle
DKS	Damus-Kaye-Stansel procedure
DORV	double outlet right ventricle
EF	ejection fraction
EC-TCPC	extracardiac total cavopulmonary connection
HLHS	hypoplastic left heart syndrome
IVC	inferior vena cava
LA	left atrium
LMWH	low molecular weight heparin
LT-TCPC	lateral tunnel total cavopulmonary connection
LA	left atrium
LPA	left pulmonary artery
LV	left ventricle
MA	mitral atresia
PA	pulmonary artery
PAP	pulmonary artery pressure
PDA	patent ductus arteriosus
PGE	prostaglandin E
PTT	partial thromboplastin time
PVR	pulmonary vascular resistance
PAIVS	pulmonary atresia with intact ventricular septum
RA	right atrium
RPA	right pulmonary artery
RV	right ventricle
SVC	superior vena cava
TCPC	total cavopulmonary connection
TOF	tetralogy of fallot
TPG	transpulmonary gradient
UAVSD	unbalanced atrioventricular septal defect
UVH	univentricular heart
UFH	unfractionated heparin
VA	ventriculoarterial
VAD	ventricular assist device
VSD	ventricular septal defect

List of Figures

List of Tables

1. INTRODUCTION

Accounting for approximately 1-2% of congenital heart defects, functionally univentricular heart (UVH) is a rare but challenging cardiac condition that requires interdisciplinary expertise (Schwedler, Lindinger et al. 2011). It is subject to complex anatomy and highly specialized surgical approaches. UVH includes a spectrum of cardiac malformations with various associated abnormalities. Although different in exact anatomy and pathophysiology, these congenital heart defects share the impossibility of biventricular surgical repair. The functional single ventricle is exposed to systemic and pulmonary circulations, resulting in total mixing of returning blood and chronic volume overload. As a result, these infants suffer from severe oxygen deprivation and changes in hemodynamics, affecting ventricular and pulmonary remodeling. (O'Leary 2002) Without early surgical palliation, mortality is high, and survival into adulthood is rare (Samanek 1992).

Fontan palliation marks a turning point in the management of these patients and is considered the primary surgical option. The purpose of univentricular heart palliation is the separation of systemic and pulmonary circulations with complete bypass of the subpulmonary ventricle. Three surgical steps are involved in achieving this hemodynamic situation.

After birth, initial stabilization and identification of the exact underlying anatomy are crucial. Stage I is intended to provide unobstructed systemic outflow and controlled pulmonary return. A systemic-to-pulmonary shunt is implanted in patients with obstructed pulmonary perfusion, while infants with pulmonary overflow benefit from a banding procedure. After initial stabilization, the bidirectional cavopulmonary shunt (BCPS) is used to partially separate pulmonary and systemic circulations. This procedure reduces volume overload on the single functional ventricle and promotes favorable remodeling.

The following Fontan operation achieves complete separation of pulmonary and systemic circulations. Although survival rates have substantially improved in recent years and Fontan completion rates have increased, certain complications remain. Elevation of systemic venous pressure and low cardiac output are the main factors leading to long-term complications. Other common issues after the Fontan procedure include protein-losing enteropathy, thromboembolisms, heart failure, and arrhythmias. (Khairy, Poirier et al. 2007)

Considering the increase of patients eligible for Fontan operation over the following years, identification and adequate management of high-risk patient groups are essential (Schilling, Dalziel et al. 2016).

1.1. Functional Univentricular Heart

1.1.1. Historical Overview

The human heart remained surgically untouched for many centuries. Wounds of the heart were considered inevitably lethal as the heart itself and the surrounding structures were too fragile to operate on. Towards the end of the nineteenth century, discussions about the operability of the heart began to spark. In 1896 English surgeon Stephen Paget wrote in his book The Surgery of the Chest*:*

> *"Surgery of the heart has probably reached the limits set by Nature to all surgery: no new method, and no new discovery, can overcome the natural difficulties that attend a wound of the heart"* (Paget 1896, p.121).

While most surgeons agreed with this opinion of Paget, there were still some attempts. In 1896 German surgeon Ludwig Rehn successfully sutured a stab wound to the right ventricle. This accomplishment greatly impacted the establishment of cardiothoracic surgery as an independent field. (Blatchford 1985)

Myths surrounding the inoperability of the heart began to shatter, and more surgeons attempted cardiac surgery. Little time passed until groundbreaking milestones defined the relatively new field in the twentieth century. During World War II, Dwight Harken successfully removed intracardiac gunmetal fragments from many wounded soldiers. He was the first to realize the importance of intensive monitoring after cardiothoracic surgery and opened the first intensive care unit in 1951. (Lefemine and Harken 1966)

The first clinical use of cardiopulmonary bypass (CPB) by John Gibbon Jr. in 1953 is considered one of the most impactful medical advances in the last century, as extracorporeal perfusion allowed for surgery on the open heart. After some initial fatalities with CPB in congenital open-heart surgery, Gibbon abandoned his invention. The routine use of CPB started with teams led by Kirklin and Lillehei, who modified the primary approach. (Hessel 2014)

Starting in the 1940s, the research of Helen Taussig and Alfred Blalock at John Hopkins Hospital paved the way for congenital heart surgery. With the Blalock-Taussig shunt, a systemic-to-pulmonary shunt, they introduced a surgical technique for treating cyanosis caused by pulmonary obstruction. (Blalock and Taussig 1984)

Muller and Dammann reported another palliative procedure for patients with increased pulmonary blood flow in 1952. By artificially narrowing the main pulmonary artery (PA)

with a band, patients with pulmonary overflow improve symptomatically. (Muller and Dammann 1952) Although these operations enhanced the quality of life, they did not address fundamental anatomical malformations of UVH patients.

In the 1950s, Glenn conducted several experimental shunts between the superior vena cava (SVC) and right pulmonary artery (RPA) on dogs. In 1958 he introduced the classic Glenn procedure after successfully operating on a seven-year-old with transposition of the great arteries (TGA) and pulmonary stenosis. (Glenn and Patino 1954)

Azzolina and Hopkins further developed this technique and introduced an end-to-side anastomosis of these vessels, now known as the BCPS (Azzolina, Eufrate et al. 1972), (Hopkins, Armstrong et al. 1985).

In 1971 Fontan presented a technique to completely separate pulmonary and systemic circulations for patients with tricuspid atresia. He connected the distal right pulmonary artery (RPA) to the SVC using the classic Glenn procedure and developed an atriopulmonary connection by anastomosing the proximal RPA to the right atrium. (Fontan and Baudet 1971)

Many modifications of this approach were attempted during the years following, including techniques by Kreutzer et al., Björk et al., and Fontan himself (Kreutzer, Galindez et al. 1973), (Bjork, Olin et al. 1979).

The total cavopulmonary connection (TCPC) has proven its worth over the initial atriopulmonary connection a decade later. It has remained the standard stage III procedure of the Fontan pathway to this day. (de Leval, Kilner et al. 1988)

The development of staged single ventricle palliation further optimized the treatment of functionally univentricular cardiac malformations, especially for high-risk patients.

Staged therapy of UVH patients with BCPS as an intermediate step was implemented into clinical practice in the 1990s. (Bridges, Jonas et al. 1990)

Gradual separation of the circulatory systems with initial BCPS followed by TCPC has been routinely performed at German Heart Center Munich (DHM) since the 1990s (Pabst von Ohain, Tonino et al. 2021).

1.1.2. Classifications

The term „univentricular heart" has been an issue of debate for many years.
UVH is defined as the inability of one ventricle to sustain either pulmonary or systemic circulation due to its lack of size and function. Both circulations are mixed at the atrial or ventricular level, resulting in severe hypoxemia and cyanosis. Hearts with functionally univentricular morphology characteristically consist of a main ventricle supporting both circulations and a second hypoplastic chamber. The accessory ventricle is typically rudimentary, as it lacks an inlet and in some cases an outlet component. To describe this anatomic malformation more adequately, the term "*functional* univentricular heart" has been introduced. (Khairy, Poirier et al. 2007)
Van Praagh introduced an approach for defining congenital cardiac malformations in 1964, focusing on the systematic description of atrial, ventricular, and arterial connections.
If each atrium is separately connected to one ventricle, the atrioventricular (AV) connection is defined as biventricular. A univentricular connection is evident when the atria predominantly drain into one ventricle through two separate or one common valve. According to this definition, hearts with atrioventricular valve atresia are excluded from the terminology. (Vanpraagh, Ongley et al. 1964)
In 1975 another definition of univentricular hearts emerged. Anderson also regarded the AV connection as essential to defining a functional UVH. The heart is defined as univentricular if the AV junction opens into a single ventricular chamber. Although a hypoplastic ventricle is typically present, it lacks an inlet component in the form of an AV connection and cannot sustain either pulmonary or systemic circulation. This classification includes tricuspid and mitral atresia. (Anderson, Becker et al. 1975)
Twenty-five years later, a nomenclature relevant to the surgical management of these patients was proposed by the committee of the *"Society of Thoracic Surgeons (STS) - Congenital Heart Surgery Database"*.
This nomenclature defines the following cardiac malformations as functionally UVH:

- double inlet left ventricle (DILV): double inlet atrioventricular connection with dominance of left ventricular morphology
- double inlet right ventricle (DIRV): double inlet atrioventricular connection with dominance of right ventricular morphology
- tricuspid atresia (TA): absence of right atrioventricular connection
- mitral atresia (MA): absence of left atrioventricular connection

- unbalanced common AV canal defect (uAVSD)
- heterotaxia
- others

(Jacobs and Mayer 2000)

Hypoplastic left heart syndrome (HLHS) is addressed in more detail in an independent classification by the *"Congenital Heart Surgery Nomenclature and Database Project"* (Tchervenkov, Jacobs et al. 2000).
Other indications for UVH palliation include extreme forms of unbalanced atrioventricular septal defect (UAVSD), pulmonary atresia with intact ventricular septum (PAIVS), Ebstein's anomaly, and congenitally corrected transposition of the great arteries (ccTGA) (Frescura and Thiene 2014).

1.1.3. Double Inlet Atrioventricular Connection

Hearts with double inlet atrioventricular connection show two atria connected to only one functional ventricle. The AV junction consists of two separate or one common AV valve, mainly supported by the dominant ventricle. As the anatomy of the AV valves is not sufficiently suggestive of either tricuspid or mitral valves, a morphological distinction is hardly possible. Thus, they are referred to as right and left atrioventricular valves. In addition to the main functional chamber, another rudimentary ventricle is typically found in the ventricular mass. A ventricular septal defect (VSD) allows blood flow to this hypoplastic chamber. Depending on underlying intracardiac morphology, double inlet left ventricle (DILV) is distinguished from double inlet right ventricle (DIRV). The walls of left ventricles (LV) are relatively smooth with fine trabeculations, and the AV valve's septal chordal attachments are typically absent. On the other hand, right ventricles are more likely to show coarse trabeculations and septal chordal attachments of the AV valve. (Khairy, Poirier et al. 2007)

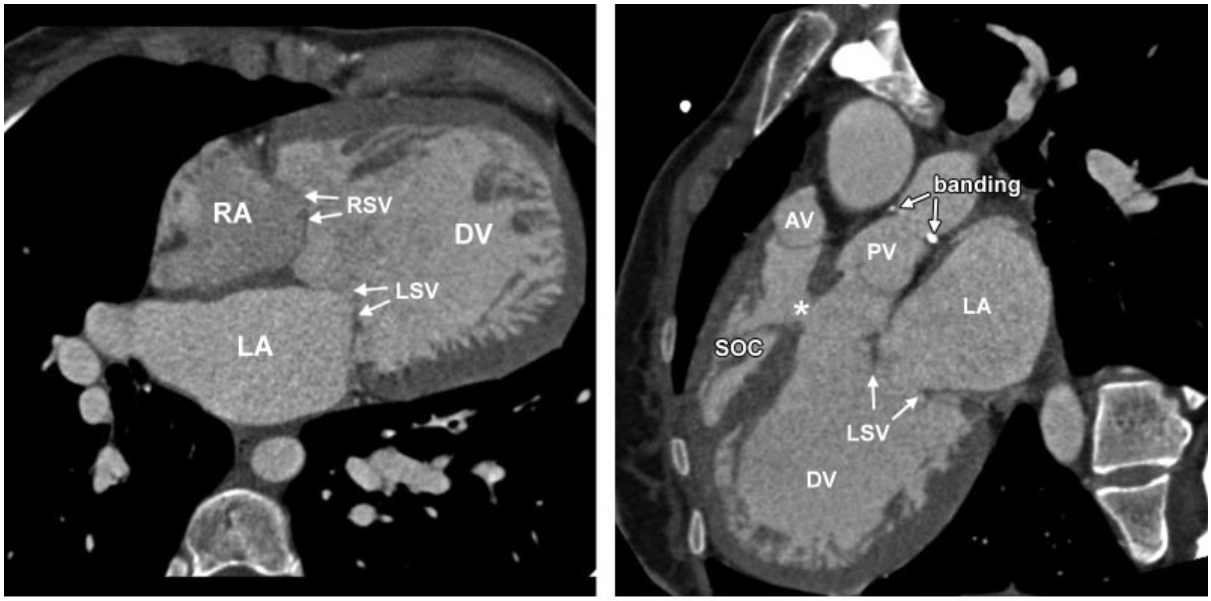


FIGURE 1. ECG-gated CT of DILV with d-TGA long axis (left) and sagittal oblique (right) (Leschka, Oechslin et al. 2007)
RA = right atrium, LA = left atrium, RSV = right-sided valve, LSV = left-sided valve, DV = dominant ventricle, AV = aortic valve, PV = pulmonary valve, SOC = subaortic outlet chamber

The more common condition is DILV, which shows a main chamber with left ventricular morphology. In most DILV cases, the ventriculoarterial (VA) connection is discordant, with the aorta exiting from the subaortic outlet chamber and the pulmonary trunk from the dominant left ventricle. *Figure 1* shows an ECG-gated CT of a 30-year-old patient with

DILV and d-TGA. Both atria are connected to the dominant ventricle via left- and right-sided valves. The aorta arises from the subaortic outlet chamber, which does not have an AV connection and receives blood from the dominant ventricle through a bulboventricular foramen. The PA appears surgically banded to limit pulmonary overflow in the sagittal oblique image. (Leschka, Oechslin et al. 2007)

Less frequently, when the great vessels are normally related, the heart is referred to as "Holmes Heart" (Weichert, Axt-Fliedner et al. 2013).

Hearts with a main ventricle of right morphology and a rudimentary left chamber are termed double-inlet right ventricles (DIRV). In a small number of cases the distinct morphology of the main chamber cannot be identified. The degree of outflow tract obstruction determines the clinical course of these patients. Double-inlet hearts with pulmonary stenosis show signs of cyanosis, whereas hearts without pulmonary restriction often present with heart failure due to pulmonary overflow. (Cook and Anderson 2006)

1.1.4. Atrioventricular Valve Atresia

Atrioventricular valve atresia is a congenital condition with a rudimentary or completely aplastic AV connection. It distinguishes right from left forms, with tricuspid atresia being the more common condition. (Dick, Fyler et al. 1975)

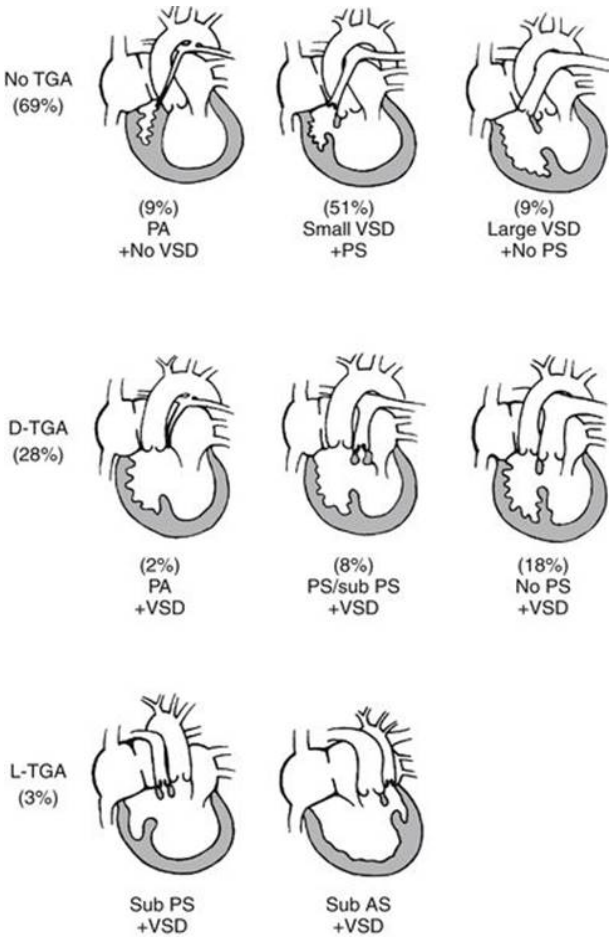
Since the right atrioventricular connection is absent, shunting on an atrial level is crucial for the survival of these children. The systemic venous return flows directly into the left atrium (LA), where it is mixed with saturated blood from the pulmonary return. The mitral valve represents the singular AV connection. In most cases, a bulboventricular foramen connects the rudimentary chamber of right morphology to the dominant left ventricle. (Minocha and Phoon 2022)

Edwards and Burchell classified tricuspid atresia in 1974 based on the VA connection (*Figure 2*). Type I refers to normally related great vessels, whereas type II implies transposition. These two major types are further divided into three subgroups depending on associated anatomical defects. In about 70% of patients with TA, the great arteries are normally related, whereas about 30% show TGA. (Tandon and Edwards 1974)

The amount of pulmonary blood flow determines clinical symptoms. It correlates with the degree of pulmonary obstruction, VSD size, and relationship of the great arteries.

Patients with pulmonary obstruction and no VSD (type Ia) rely on ductal patency to maintain sufficient pulmonary perfusion. In types I a/b and II a/b, pulmonary obstruction results in early cyanosis and hypoxemic seizures. On the other hand, patients without pulmonary obstruction and VSD (type c) are more likely to show signs of heart failure, tachypnea, and respiratory distress due to pulmonary overflow.

Depending on the specific subtype, different stage I procedures are performed. A shunt is implanted in patients with reduced pulmonary blood flow, whereas increased pulmonary blood flow is addressed with pulmonary artery banding. Stage II and stage III operations are planned according to the institutional policy. (Minocha and Phoon 2022)



I. Normally related great arteries

a. pulmonary atresia, no VSD
b. pulmonary stenosis and/ or restrictive VSD
c. no pulmonary stenosis and non-restrictive VSD

II. Transposition of the great arteries (D-TGA)

a. pulmonary atresia and VSD
b. pulmonary stenosis/hypoplasia and VSD
c. no pulmonary stenosis and VSD

III. Transposition of the great arteries (L-TGA)

FIGURE 2. Classification of Tricuspid Atresia by Edwards and Burchell (Park 2020)
TGA = transposition of the great arteries, PS = pulmonary valve stenosis, VSD = ventricular septal defect

An absent AV connection or imperforate valvular membrane causes left AV valve atresia. It often manifests as part of hypoplastic left heart syndrome (HLHS) with aortic atresia and left ventricular hypoplasia. To provide adequate drainage of the pulmonary venous return, left-to-right shunting through an ASD is mandatory. Large ASDs often result in right ventricular hypertrophy due to massive overflow. Systemic perfusion is secured through shunt connections on the ventricular level. The clinical presentation is determined by the kind and severity of concomitant defects, including symptoms like cyanosis, congestive heart failure, and respiratory difficulties. (Aliyu, Gambo et al. 2015)

1.1.5. Hypoplastic Left Heart Syndrome

HLHS is a congenital cardiac condition characterized by multiple closely related malformations affecting the left heart and the aorta. Atresia of the mitral and aortal valves, as well as hypoplasia of the left ventricle, ascending aorta, and aortic arch, are suggestive of this disease. *Figure 3* illustrates the anatomy of HLHS (Yabrodi and Mastropietro 2017). It demonstrates the underdevelopment of the left-sided heart, resulting in a dependency on open shunt connections to provide adequate perfusion. Saturated blood from the pulmonary veins drains into the left atrium and follows the left-to-right shunt connection to the RA. The RV ejects the systolic volume into the pulmonary artery. Through this main outlet vessel, pulmonary- and systemic circulations are maintained. The systemic perfusion relies on a patent arterial duct, connecting the PA to the aorta. This shunt connection provides adequate perfusion into the lower body and retrogradely into the myocardial and cerebral arteries. In some cases, additional malformations, like coarctation of the aorta (CoA), are present. An enlargement of the right ventricle and pulmonary artery is observed in many cases due to volume overload. (Feinstein, Benson et al. 2012)

Due to ductal-dependent systemic circulation, postnatal prostaglandin E1 (PGE) infusions are required to prevent cardiogenic shock. Despite the variety of possible malformations, diagnosis of HLHS indicates definite Fontan palliation without the possibility of biventricular repair. After initial stabilization, Norwood procedure is the first part of staged palliation for HLHS, followed by stage-II procedure and Fontan operation. (Gobergs, Salputra et al. 2016)

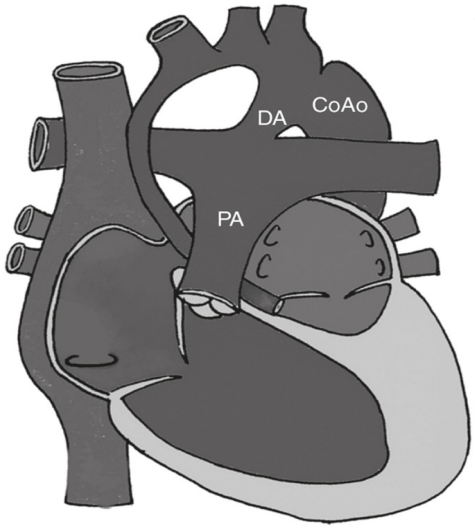


FIGURE 3. Hypoplastic Left Heart Syndrome (Yabrodi and Mastropietro 2017)
PA = pulmonary artery, DA = ductus arteriosus, CoAo = coarctation of aorta

1.1.6. Unbalanced Atrioventricular Septal Defect

The atrioventricular septal defect (AVSD) is characterized by atrial and ventricular septal defect, as well as AV valve malformation. AVSD is divided into partial, complete, and intermediate forms. Partial AVSD shows an ostium primum defect and various degrees of AV valve regurgitation without septal defect on the ventricular level. Additional ventricular communication via a small restrictive VSD distinguishes intermediate from partial forms of AVSDs. Patients with complete AVSD present with a large ventricular septal defect and common AV valve, that overrides both ventricles. (Jacobs, Burke et al. 2000)

Another distinction emphasizes ventricular balance. Balanced AVSD is more common, with the atrioventricular valve aligned equally over the ventricles. Relevant to univentricular palliation are unbalanced forms of AVSD (UAVSD), which occur in about 10% of AVSD cases. Unequal alignment of the AV-junction plays an important role in the underdevelopment of either left or right ventricle and ultimately in the decision-making between biventricular or univentricular repair. Right or left ventricular dominance is observed in hearts with UAVSD, as well as concomitant obstruction of systemic or pulmonary outflow. With large numbers of patients having associated cardiac and non-cardiac comorbidities, the treatment of UAVSD becomes increasingly complex. (Overman, Dummer et al. 2013)

The severity of the defect and any related abnormalities determine clinical symptoms. Patients with severe left-to-right shunting develop signs of pulmonary congestion and right heart failure, including tachypnea, hepatomegaly, and failure to thrive. Depending on the volume overload on either ventricle, left or right ventricular valve insufficiency is likely to develop over time. Increased flow to the lungs leads to an overload of the pulmonary vascular system and ultimately to elevation in pulmonary vascular resistance. (Craig 2006)

1.1.7. Natural History

Since most patients with UVH receive palliative operations during infancy, no current data exists investigating the natural history. Considering the heterogeneity of UVH pathologies, the natural course varies. Only a few studies in the 1980s and early 1990s investigated unoperated patients with UVH. In 1984 Moodie et al. analyzed the outcomes of 83 patients with UVH who did not undergo palliative surgery. The annual mortality rate was 4.8 %. By age 16, 70% of patients with dominant left ventricle pathologies died because of arrhythmia, congestive heart failure, or sudden cardiac death. Worse results were reported for patients with dominant right ventricle pathologies, where a 4-year mortality rate of 50% was observed. **(**Moodie, Ritter et al. 1984**)**

Another study from 1990 shows the natural history of 90 patients diagnosed with functional UVH. The results were similarly adverse, with a 62.5 % mortality rate during the 9.5 years observation period. The natural course of patients with tricuspid atresia varies, depending on the amount of pulmonary blood flow. In patients with TA and VA concordance, pulmonary perfusion is limited due to the presence of a restrictive bulboventricular foramen. Upon narrowing of the foramen, non-surgically treated patients suffer from severe hypoxemia. (Frontera Izquierdo and Cabezuelo Huerta 1990)

Šamánek et al. investigated the natural survival of children with CHDs during a 27-year period in Central Bohemia. Among all included congenital malformations, univentricular pathologies had the highest risk of mortality during the first year of life. Thirty-nine percent of patients diagnosed with HLHS died within the first week. Survival beyond the first month of life was only observed in patients with milder variants of the malformation. (Samanek 1992)

All three studies concluded that early palliative surgeries improve the natural history and prognosis of patients with UVH. These adverse outcomes for patients with functionally UVH led to innovative surgical strategies, most notably Fontan's atriopulmonary anastomosis for treating tricuspid atresia (Fontan and Baudet 1971).

1.1.8. Pathophysiology

The altered hemodynamics of functionally UVH result in profound changes in physiology. Inflow or outflow tract obstruction, systemic and pulmonary return alterations, AVVR, and communication across the septum are essential factors determining UVH physiology. Exemplarily, HLHS with systemic outflow obstruction is shown in *Figure 4*. Due to the underdevelopment of the left ventricle and mitral valve, open shunt connections are crucial during infancy. Returning blood from the lungs drains into LA, followed by left-to-right shunting through an ASD into the RA. Due to systemic outflow obstruction, mixed blood follows through the pulmonary artery, and systemic perfusion is maintained via a PDA. On the contrary, patients with pulmonary obstruction typically show left-to-right shunting through the PDA to maintain pulmonary perfusion. (Feinstein, Benson et al. 2012)

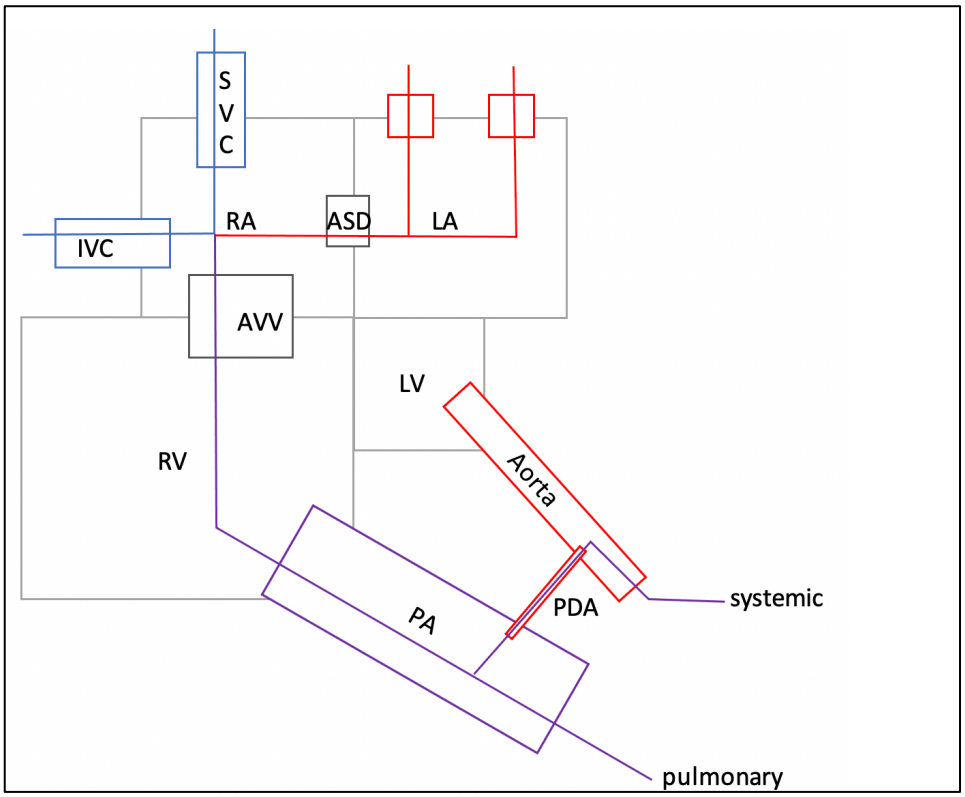


FIGURE 4. Hypoplastic Left Heart Syndrome before Fontan Palliation
IVC = inferior vena cava, SVC = superior vena cava, ASD = atrial septal defect, RA = right atrium, LA = left atrium, AVV = atrioventricular valve, RV = right ventricle, LV = left ventricle, PA = pulmonary artery, PDA = patent ductus arteriosus
blue = desaturated blood, red = saturated blood, purple = mixed blood

Chronic volume overload of the single functional chamber has multiple pathophysiological consequences. AV valve regurgitation and heart failure are common effects over time. (Sharma 2000)

Another aspect of UVH pathophysiology is decreased oxygen saturation, resulting in end-organ dysfunction. The mixture of deoxygenated blood from the systemic venous return and oxygenated pulmonary venous blood reduces the total oxygen saturation. This condition is aggravated by pulmonary obstruction. Combined with the low cardiac output of the single ventricle, oxygen distribution to end organs deteriorates. These changes in physiology contribute to impaired gastrointestinal and neurologic functions observed in single ventricle patients. (Ricci, Lombardi et al. 2005)

BCPS and TCPC result in profound changes in hemodynamics. The principle for sufficient pulmonary and systemic perfusion in UVH patients is the complete separation of both pathways. As visualized in *Figure 5*, the single functional ventricular chamber is transformed into the systemic ventricle. After total separation of pulmonary and systemic pathways, central venous blood passively flows into the pulmonary circuit. These hemodynamic changes result in ventricular volume unloading and provide adequate pulmonary perfusion. Saturations rise to 85 % after BCPS and reach even higher numbers after Fontan completion. (Stumper and Penford 2017)

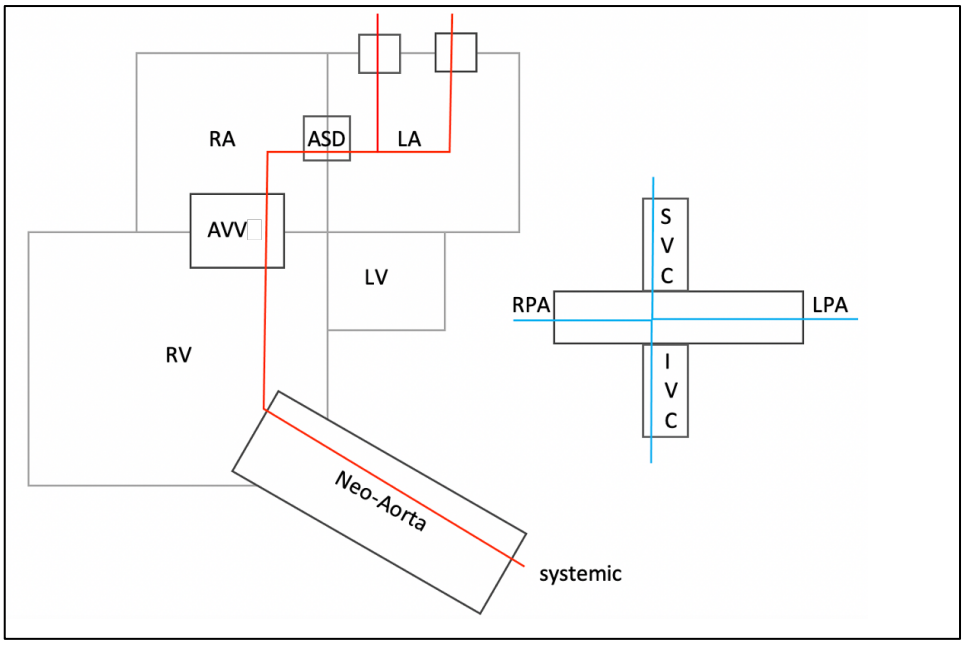


FIGURE 5. Hypoplastic Left Heart Syndrome after Fontan Palliation
IVC = inferior vena cava, SVC = superior vena cava, ASD = atrial septal defect, RA = right atrium, LA = left atrium, AVV = atrioventricular valve, RV = right ventricle, LV = left ventricle, PA = pulmonary artery, PDA = patent ductus arteriosus, RPA = right pulmonary artery, LPA = left pulmonary artery; blue = desaturated blood, red = saturated blood, purple = mixed blood

1.2. Surgical Management

Several cardiac malformations without the possibility of biventricular surgical repair are considered indications for univentricular palliation. The primary aim is the separation of pulmonary and systemic circulations, eventually achieved by complete bypass of the subpulmonary ventricle after TCPC. The staged palliation approach involves preceding palliative procedures to maintain good ventricular function and low pulmonary vascular resistance. Additional cardiac malformations are also addressed during earlier stages of the Fontan pathway.

As illustrated in *Figure 6*, all three stages include different options depending on individual cardiac morphology. The following chapters will detail the surgical process of staged Fontan palliation by the Department of Congenital and Pediatric Heart Surgery standards at German Heart Center Munich.

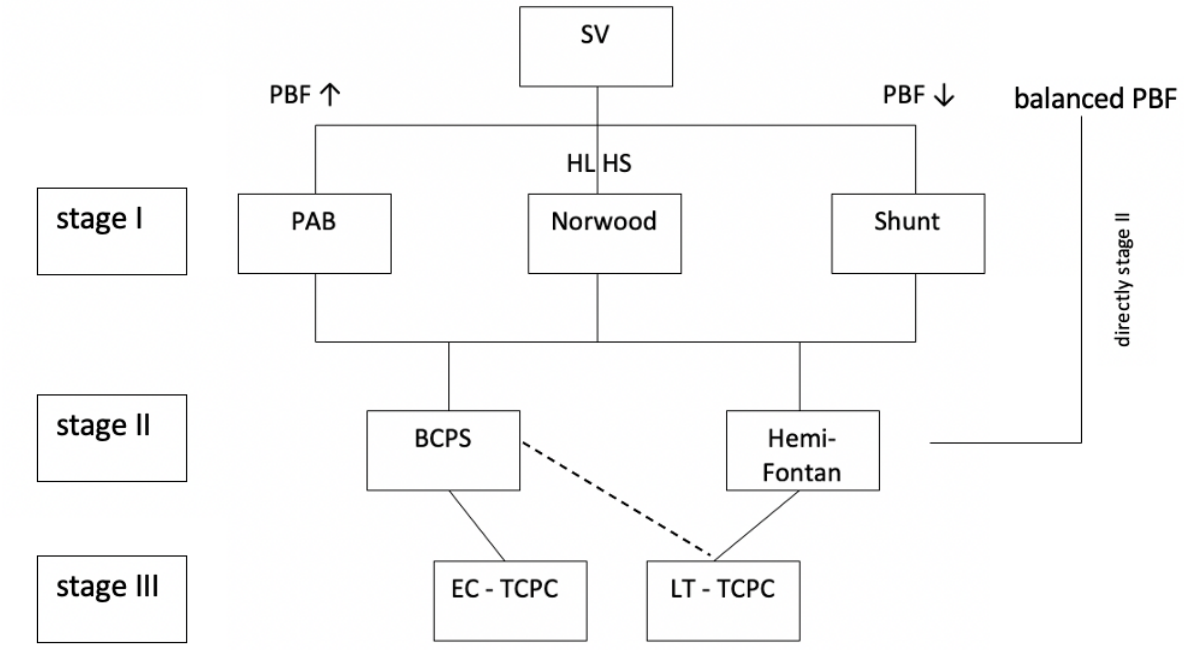


FIGURE 6. Staged Univentricular Heart Palliation Pathway
PBF = pulmonary blood flow, SV = single ventricle, PAB = pulmonary artery banding, EC-TCPC = extracardiac total cavopulmonary connection, LT-TCPC = lateral tunnel total cavopulmonary connection, HLHS = hypoplastic left heart syndrome

The start and finish of pediatric cardiac surgery consist of a few routine steps, which are standardized for all operations. Median sternotomy, initiation of CPB, weaning from CPB, hemostasis, and sternal closure are of substantial importance for the surgical result and are thus described in the following.

Initiation of CPB in neonates and children requires excellent expertise and interdisciplinary coordination. Different options for extracorporeal circulation are available depending on the child's age, weight, height, and anatomical features. Most procedures of staged UVH palliation demand CPB to adequately visualize relevant structures and oxygenate the patient's blood while operating on the heart. Before CPB initiation, 250-450 U/kg heparin is administered to prevent any clotting caused by contact of CPB surfaces with the patient's blood. Adequate anticoagulation is measured by the activated clotting time (ACT). Once the ACT reaches values above 450 seconds, vascular cannulation is possible. (Gruenwald, Manlhiot et al. 2010)

Venous cannulas are inserted in both caval veins or RA to drain returning systemic blood. Additional vents might be placed to ensure a bloodless surgical field and optimize visualization. CPB machines consist of a roller pump, heat exchanger, oxygenator, and filter. Drained venous blood passes through these compartments and returns to the patient's system via an arterial cannula, typically placed in the ascending aorta. Throughout the surgery, the ACT is measured to optimize the heparin administration. (Sarkar and Prabhu 2017)

Surgery on the aortic arch is typically performed with selective antegrade perfusion to ensure adequate brain protection. Norwood operation with the construction of a neo-aorta is conducted in this fashion. (Vricella, Samankatiwat et al. 2004)

While some procedures require cardiac arrest, others are performed on the beating heart. Intracardiac procedures, for example, AVVR repair, typically require cardioplegia to achieve electromechanical cardiac arrest. After arterial cannulation, CPB flow is temporarily stopped, followed by aortal clamping. Patients with intact aortic valves receive antegrade cardioplegic infusion through the aortic root. Direct injection into the coronary ostium is preferred in patients with aortic valve insufficiency. Another option is retrograde infusion via the coronary sinus. After the core surgery, the heart is de-aired, and the aortic cross-clamp, if present, is released. The operative result is analyzed via transesophageal echocardiography by either the anesthesiologist or a pediatric cardiologist. If the result is adequate and the heart has regained normal rhythm and contractility, the patient is weaned from CPB. All patients receive temporary ventricular and atrial pacing wires to guarantee good rhythm. In close consultation with the perfusionist, venous cannulas and vents are removed. Protamine is

administered prior to the removal of the arterial line, and the ACT is measured. Subsequently, the aorta is decannulated. Before sternal closure, chest drains are inserted to remove blood or fluid from the pleura, pericardium, or mediastinum after the operation. Successful hemostasis is necessary before the sternum is approximated and the skin is closed. (Sarkar and Prabhu 2017)

1.2.1. Perinatal Management

Definite palliation with complete separation of the pulmonary and systemic circulation is the primary surgical goal for UVH patients. During the perinatal period, identifying the underlying anatomy and stabilization of the newborn is essential. Maintaining unobstructed systemic outflow and balanced flow to the lungs is crucial. In general, blood flow depends on shunt connections if either pulmonary or systemic outflow is obstructed. Obstruction of the pulmonary outflow tract results in left-to-right shunting through the ductus arteriosus, while right-to-left shunting is observed in patients with systemic outflow obstruction. Suppose the PDA closes postnatally, patients with ductal-dependent pulmonary circulation present with hypoxemia and respiratory distress. Upon PDA closure, signs of congestive heart failure and decreased multiorgan perfusion are observed in patients with ductal-dependent systemic circulation. Until further interventions are conducted, ductal-dependent newborns receive intravenous PGE infusions to preserve the patency of the duct. During neonatal intensive care, staged surgical reconstruction and preceding interventional procedures are discussed. Patients without the possibility of biventricular repair are considered for staged palliation. (Davies and Pizarro 2015)

1.2.2. Stage I

Due to the variety of diagnoses, there are different surgical approaches during infancy. A systemic-to-pulmonary shunt is implanted in patients with obstructed pulmonary outflow, whereas conditions with increased pulmonary blood flow are met with banding. Hypoplastic left heart syndrome and its variants with systemic outflow obstruction are addressed with a unique surgery, the Norwood procedure. (Biglino, Giardini et al. 2013)

Decreased Pulmonary Blood Flow

Neonates with reduced pulmonary blood flow due to atresia or obstruction of the PA typically present with severe hypoxemia. A good example is tricuspid atresia with normally related great vessels, in which a restrictive VSD or pulmonary stenosis prevents adequate lung perfusion. Additional blood flow to the lungs is required to provide sufficient pulmonary circulation. The modified Blalock-Taussig (*Figure 7A*) shunt is the most used systemic-to-pulmonary artery shunt that secures adequate saturation. A polytetrafluoroethylene graft connects the innominate artery to the right pulmonary artery. (Blalock and Taussig 1984)
After performing median sternotomy and resecting parts of the infantile thymus, the right innominate artery is identified and mobilized. After partially clamping the innominate artery, a longitudinal incision is made. A polytetrafluoroethylene graft is connected to the innominate artery with a monofilament suture. After completing the anastomosis, the clamp is removed from the innominate artery and placed on the graft, which is cut to the appropriate length. The right pulmonary artery is isolated and partially clamped. After performing longitudinal arteriotomy, the graft is anastomosed to the pulmonary artery with non-resorbable sutures. Prior to removing the clamp, the persistent arterial duct is temporarily occluded to examine adequate pulmonary blood flow through the constructed shunt. The duct is ligated if saturation between 75 and 85 % is observed. In selected patients in whom the innominate artery is not functional as proximal anastomosis, a central shunt (*Figure 7C*) is performed. Ascending aorta is used as proximal anastomosis. Another option providing adequate pulmonary blood flow is the Sano shunt, which involves a right ventricle to pulmonary artery connection (*Figure 7B*).
Ascending aorta to right pulmonary artery anastomosis (Waterston-Cooley shunt) and descending aorta to left pulmonary artery anastomosis (Pott shunt) are obsolete.
(Lange and Horer 2010)

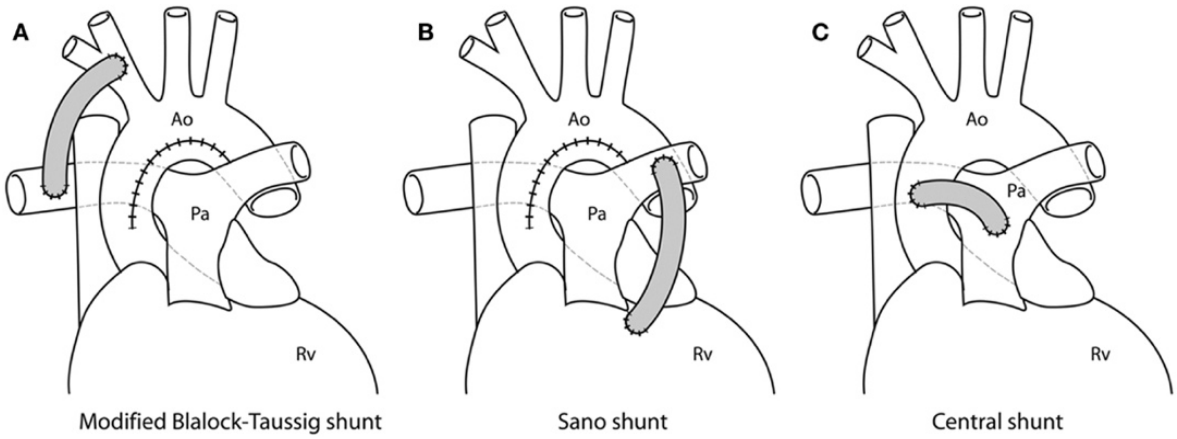


FIGURE 7. Different Shunting Options during Stage I (Biglino, Giardini et al. 2013)

Increased Pulmonary Blood Flow

Cardiac malformations associated with excessive pulmonary blood flow often result in pathologic changes in the pulmonary vasculature, pulmonary hypertension, and pulmonary vascular resistance (PVR) elevation. Many patients with UVH experience pulmonary overflow because of massive left-to-right shunting. Pulmonary artery banding is performed in these patients to decrease cardiac volume load and pulmonary artery pressure. (Agasthi and Graziano 2021)

After median sternotomy and partial resection of the thymus, the ascending aorta is separated from the pulmonary trunk. The band is placed around the MPA with careful attention to the pulmonary valve and pulmonary branches. Saturation and pressure in the distal PA and systemic circulation are observed. By placing clips or sutures on the band, the circumference is adjusted, preferably achieving a pressure gradient between 30 and 60 mmHg. PAB is performed according to Trusler's formula for the initial assessment of the diameter of the tape. Adequate tightening of the band is determined if mean pulmonary artery pressure is less than 25mmHg and oxygen saturation was maintained at greater than 80% on a 21% fraction of inspired oxygen. It is essential to avoid hypoxemia and, at the same time, achieve adequate pulmonary artery pressure. (Lange and Horer 2010)

Norwood Procedure

Hypoplastic left heart syndrome is a condition that involves the underdevelopment of several structures of the left heart, including the mitral valve, aortic valve, left ventricle, and aorta. To optimize Fontan candidacy, HLHS patients undergo Norwood palliation during the neonatal period. Typically conducted during the first week of life, the Norwood procedure aims to provide unobstructed systemic blood flow while creating a restrictive source of pulmonary blood flow.

The procedure involves three steps: Aortic arch reconstruction, atrioseptectomy, and shunt placement. (Feinstein, Benson et al. 2012)

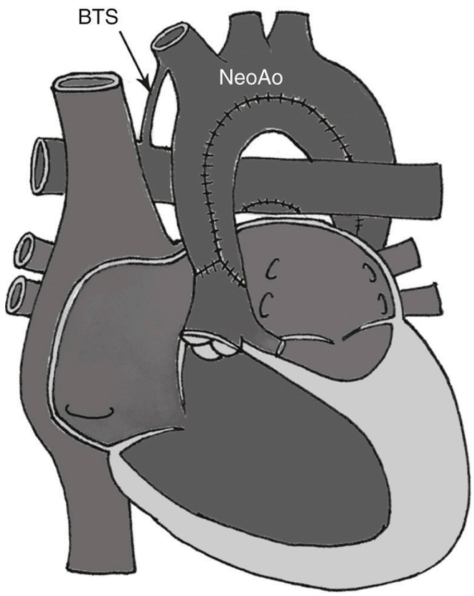


FIGURE 8. Norwood Procedure for Hypoplastic Left Heart Syndrome (Yabrodi and Mastropietro 2017)
BTS = Blalock-Taussig shunt, NeoAo = Neo Aorta

Following median sternotomy and partial resection of the thymus, cardiopulmonary bypass is initiated. After cannulation of the pulmonary artery, venous cannulas are placed in both caval veins. Selective cerebral perfusion is performed, and cardioplegia is injected.

The first step provides unobstructed systemic blood flow and requires aortic cross-clamping followed by aortal reconstruction. After resection of the pulmonary root and the arterial duct, the hypoplastic aorta is longitudinally incised from descending, through the aortic arch, to ascending. Then, the neo-aorta is constructed by suturing the proximal end of the pulmonary trunk to the native aorta via a pulmonary homograft or auto-pericardium. This achieves a connection between the single functional ventricle and the systemic circulation.

After performing atrial septectomy, the arterial cannula is placed into the neo-aorta, and the aortic cross-clamp is released. The second step involves the establishment of a restrictive source of pulmonary blood flow. This is accomplished by either using the modified BT shunt or the Sano shunt to create a systemic-to-pulmonary artery connection. (Lange and Horer 2010)

Hybrid Procedure

Even though the Norwood procedure has become the preferred method of care for infants diagnosed with HLHS, its complexity and the requirement of CPB demand clinical stability of the neonate. Initially described in 1993 by Gibbs et al., the hybrid procedure has emerged as a less invasive stage I option for patients with HLHS and its variants. Combining off-pump surgery with interventional catheterization, this interdisciplinary approach accomplishes similar physiological goals as the Norwood operation. To decrease excessive pulmonary blood flow and increase systemic perfusion, left and right pulmonary arteries are banded. Through interventional stent placement, patency of the arterial duct and hereby adequate systemic perfusion is ensured. To permit unrestricted interatrial communication, surgical or interventional atrial septectomy is performed. After the hybrid procedure, patients are either palliated with further stages of the Fontan pathway or considered for cardiac transplantation. (Yabrodi and Mastropietro 2017)

Systemic Outflow Tract Obstruction

For patients with obstructed systemic outflow, different initial procedures are necessary. Aortic arch coarctation with hypoplasia or stenosis is reconstructed with a coarctation procedure and concomitant pulmonary artery banding, if necessary. Another method for infants with systemic outflow tract obstruction is the Damus-Kaye-Stansel (DKS) procedure. DILV and tricuspid atresia with subaortic obstruction are indications for performing this procedure. If the aorta exits from the rudimentary ventricle, which is connected to the dominant ventricle through a restrictive bulboventricular foramen, anastomosis of the ascending aorta to the PA using the DKS procedure is an option for primary palliation. (Laks, Gates et al. 1992)

1.2.3. Stage II

Univentricular hearts are subject to excessive volume load due to parallel pulmonary and systemic circulation. The second stage was implemented as an intermediate step before Fontan completion to reduce the volume work of the systemic ventricle and to provide adequate pulmonary blood flow.

After successful stage I palliation, the procedure should be conducted at three to six months of age. The operation is performed when the pulmonary vascular system has sufficiently developed, and the pulmonary vascular resistance has decreased to withstand hemodynamic changes. Residual cardiac anomalies are addressed during this stage to improve the hemodynamic situation further. Concomitant procedures vary depending on the underlying anatomy and include repair of the AV valve, reconstruction of the pulmonary artery, DKS anastomosis, and repair of anomalous pulmonary venous return. (Barron, Haq et al. 2017)

With the aim of partially separating pulmonary and systemic circulation, two techniques are differentiated: the bidirectional cavopulmonary shunt and the Hemi-Fontan procedure. The basic principle is partial cavopulmonary anastomosis by passively directing deoxygenated blood from the SVC into the pulmonary vasculature- bypassing the single ventricle. Pulmonary inflow is driven by the SVC-RPA pressure gradient instead of ventricular efficiency. Institutional preferences and intentions on how to complete Fontan circulation determine the decision-making between BCPS and Hemi-Fontan. While the BCPS procedure is better suited for extracardiac Fontan completion, Hemi-Fontan operation is preferred when planning lateral tunnel TCPC as the third stage. Both procedures are performed using cardiopulmonary bypass. A disadvantage of Hemi-Fontan is the requirement of cardioplegic cardiac arrest and aortic cross-clamping, whereas BDG can be performed on a beating heart. On the other hand, augmentation of the pulmonary arteries, which is done during the HF procedure, allows correction of possible PA stenosis, which could facilitate the completion process in the future. (Talwar, Nair et al. 2014)

At DHM, the preferred option is BCPS, followed by extracardiac total cavopulmonary connection.

Bidirectional Cavopulmonary Shunt

Partial cavopulmonary anastomosis by means of the BCPS procedure is achieved by suturing the distal SVC to the superior surface of the RPA, as visualized in *Figure 9* (Jonas 2011). The use of CPB during the operation is optional. Off-pump BCPS is a possibility for patients without concomitant intracardiac procedures. It requires a shunt connection from the SVC or innominate vein to the RA under systemic heparinization. (Liu, Lu et al. 2004)

The following technique includes the support of CPB. Midline sternotomy is the standard approach for this operation. After mobilization of the SVC and ascending aorta, the azygos vein is ligated to prevent collateral blood flow to the IVC. After heparinization, the ascending aorta or the neo-aorta is incised for arterial cannulation. Venous cannulas are placed in the RA and distal SVC, followed by initiation of the CPB. If present, the systemic-to-pulmonary artery shunt is divided to prevent additional blood flow to the lungs.

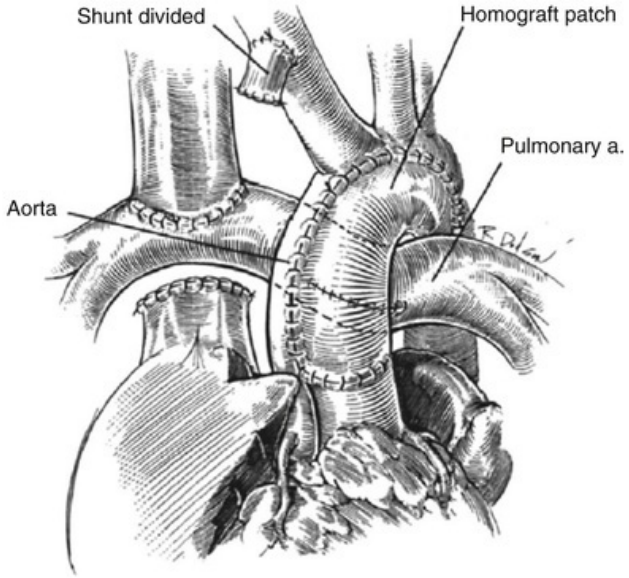


FIGURE 9. Bidirectional Cavopulmonary Shunt (Jonas 2011)

After temporarily occluding the SVC proximal to the previously inserted bypass cannula, it is clamped above the junction to the right atrium. Subsequently, the SVC is divided, and its cardiac end is oversewn. After mobilizing and clamping the RPA, a transversal incision is made on the superior surface. If the patient received a BT-shunt prior to BCPS, the pulmonary end is removed, and the incision is enlarged. By using monofilament absorbable sutures, the SVC-RPA anastomosis is performed. Bilateral BCPS is performed if a left SVC is present, by connecting the left SVC to the LPA in the same fashion described above.

The patient is then weaned from CPB while carefully monitoring hemodynamic parameters as well as the oxygen saturation. (Lange and Horer 2010)

Hemi-Fontan Procedure

As with BCPS, the goal of the Hemi-Fontan procedure is the optimal preparation for Fontan completion. Median sternotomy is the standard approach for this procedure. After initiation of CPB, the aorta or neo-aorta is clamped and, contrary to BCPS, electromechanical cardiac arrest is achieved via cardioplegic infusion. Antegrade pulmonary blood flow is prevented by ligating the cardiac end of the pulmonary trunk as well as systemic-to-pulmonary artery shunts if present. After right atriotomy and extension of the incision to the medial side of the SVC, the RPA is incised. The incision is continued leftward to the origin of the left upper lobe branch. Any narrowing of the pulmonary arteries is augmented during this procedure. (Talwar, Nair et al. 2014) As shown in *Figure 10A*, a monofilament suture is used to connect the posterior part of the incised SVC to the rightward edge of the pulmonary arteriotomy. A triangular homograft patch is then sutured to the leftward edge of the pulmonary arteriotomy, continued rightward to the SVC and incised RA. By creating a dam between the SVC and RA, blood flow from the SVC to the RA is interrupted and partial cavopulmonary separation is achieved. The surgical result and blood flow pattern are visualized in *Figure 10B*. At the time of Fontan completion, the previously sewn-in patch between the SVC and RA is excised. Total cavopulmonary separation is achieved by subsequent lateral tunnel intracardiac Fontan technique. A polytetrafluoroethylene (PTFE) graft is placed between the IVC and excised dam to redirect inferior caval blood to the pulmonary arteries. (Spray 2013)

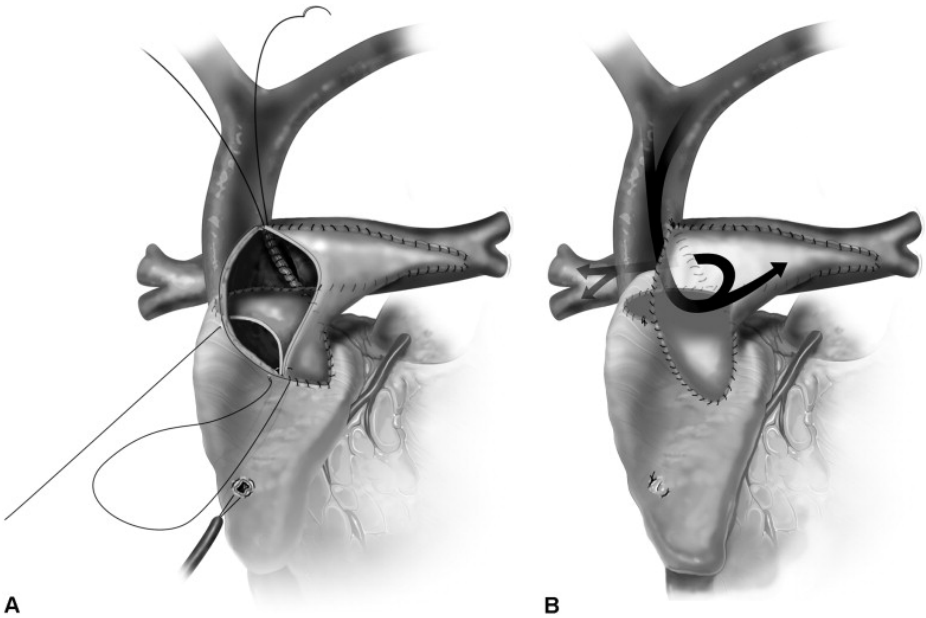


FIGURE 10. Hemi-Fontan Procedure (Spray 2013)

1.2.4. Stage III

The classic Fontan operation for the surgical management of functional UVH was introduced in 1971 (Fontan and Baudet 1971). Originally performed as a direct RA-PA anastomosis, it was further modified and eventually replaced by the total cavopulmonary connection (de Leval, Kilner et al. 1988).

After partially directing central venous blood into the pulmonary circulation after BCPS, the IVC is connected to the RPA during the final stage, restoring in-series circulation. Fontan completion reduces ventricular volume overload and increases arterial saturation by completely separating systemic output and pulmonary venous drainage. At DHM, TCPC is routinely performed between 18 and 24 months of age, and at a body weight of 10 kg or more. (Ono, Kasnar-Samprec et al. 2016)

The last operation of the Fontan pathway is performed using either the lateral tunnel or extracardiac conduit technique (*Figure 11*). If stage II was performed using BCPS, Fontan is generally completed using an extracardiac conduit. On the contrary, if the patient underwent HF procedure, lateral tunnel TCPC is preferred. (Kogon 2012)

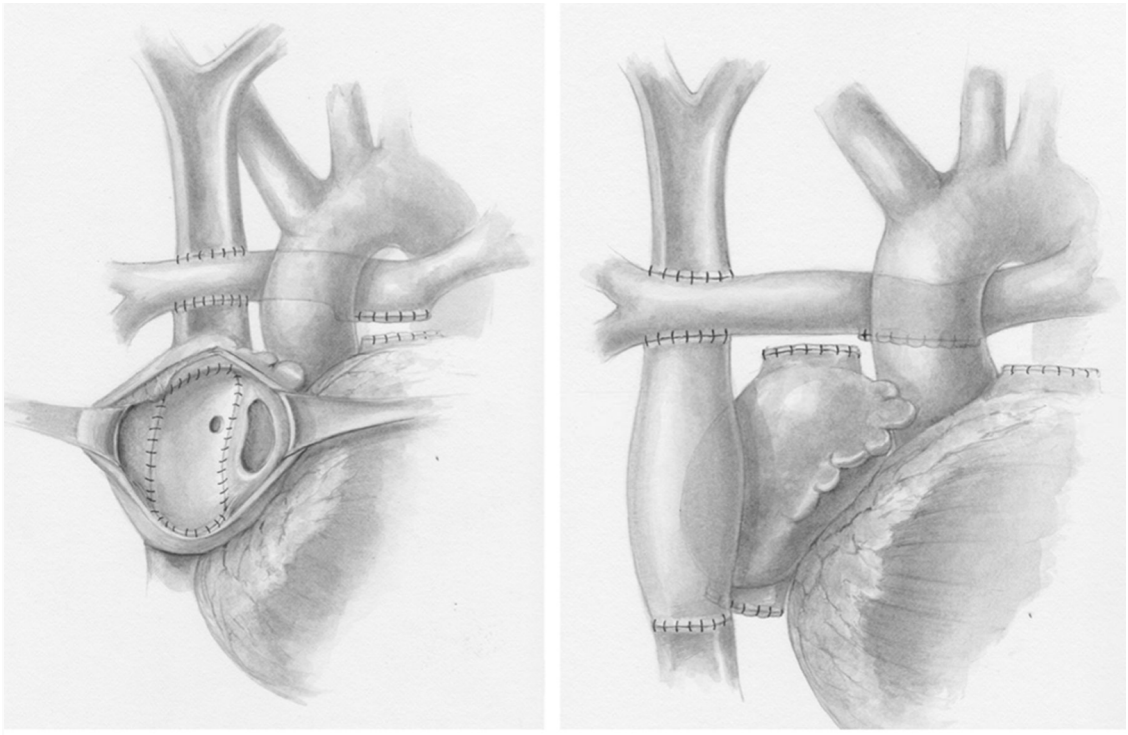


FIGURE 11. Lateral Tunnel vs. Extracardiac Fontan (Kogon 2012)

Extracardiac Conduit Total Cavopulmonary Connection (EC-TCPC)

Following median sternotomy, relevant cardiac structures are dissected free.
Both caval veins and the aorta are exposed for cannulation. Right and proximal left pulmonary arteries are mobilized. After heparinization, the aorta is cannulated. Venous cannulas are placed in the SVC and IVC. The procedure is usually performed in normothermia without cardiac arrest.
After initiation of cardiopulmonary bypass, the SVC is snared and the pulmonary arteries are temporarily clamped. The right pulmonary artery is incised on the inferior surface, opposite the superior cavopulmonary anastomosis. A Gore-Tex tube graft is anastomosed to the RPA in an end-to-side fashion. The tube size ranks from 14 to 20 mm, whereas 18 mm is the most frequently used size at DHM (Ono, Kasnar-Samprec et al. 2016).
After the anastomosis is completed, clamps and snares are removed, and the graft is temporarily clamped. Then, the IVC is snared proximal to the venous cannula and clamped above the junction to the right atrium. After dividing the vein, the cardiac end is oversewn using monofilament absorbable sutures. The conduit is then trimmed to the correct size and sutured to the transected IVC in an end-to-end fashion. (Lange and Horer 2010)
If the conduit does not distort the RPA, snares and clamps are removed, and the patient is slowly weaned from CPB. After the hemodynamic assessment, a 4mm fenestration is created in high-risk patients. Fenestration provides an artificial right-to-left shunt, which lowers central venous pressure and improves the cardiac output. (Marcelletti, Corno et al. 1990)
Extracardiac TCPC is the preferred option at DHM since 1999, following its superiority over the lateral tunnel technique in some in-house studies (Schreiber, Kostolny et al. 2004).

Lateral Tunnel Total Cavopulmonary Connection (LT-TCPC)

As with EC-TCPC, the operative approach is median sternotomy, followed by CPB initiation and cardioplegic cardiac arrest. An incision is made in the right atrial appendage and the Hemi-Fontan patch is exposed. After removing the patch between the SVC and right atrium, an intraatrial lateral tunnel is created. The Gore-Tex tunnel, which is cut to size and sutured into the right atrium, baffles the blood from the IVC to the pulmonary artery. If fenestration is indicated, a 4mm incision is made in the inferior cavopulmonary baffle. After deairing the heart, the patient is slowly weaned from cardiopulmonary bypass. (de Leval, Kilner et al. 1988)

1.2.5. Surgical Alternatives

The current standard of treatment for UVH is staged Fontan palliation. For infants with a high risk for mortality during multistage surgical palliation, primary cardiac transplantation offers a curative alternative. The sacristy of donors, organ rejection, and complications following transplantation are limiting factors of this procedure. Whilst awaiting cardiac transplantation, almost 20% of infants die. (Rao 2019)

Several surgical methods as a bridge to transplantation may be considered to minimize waitlist mortality. Ruiz et al. published their results with ductal stenting in 1993 (Ruiz, Gamra et al. 1993), and Mitchell et al. described their experience with bilateral PAB in 2003 (Mitchell, Campbell et al. 2003). Combining ductal stenting with bilateral PA banding, the hybrid procedure is another alternative to reduce irreversible changes to the pulmonary vascular system prior to cardiac transplantation (Morray, Albers et al. 2018).

Another possible bridging option is the implantation of a ventricular assist device (VAD). Especially patients with heart failure and other severe cardiac risk factors profit from bridging with VAD insertion. (Bleiweis, Fudge et al. 2022)

After successful transplantation, various immunosuppressants are required to avoid graft rejection. Moreover, regular outpatient consultations and endomyocardial biopsies are crucial in the early detection of organ rejection. (Rao 2019)

1.3. Objective

Individuals with UVH pathologies represent a population with great anatomical and pathophysiological complexity. Parallel supply of systemic and pulmonary circulation by the single functional ventricle results in volume overload, AVV regurgitation, and deterioration in end-organ oxygen distribution. Fontan palliation allows the separation of these pathways by creating an in-series circulation and hereby reducing the chronic volume overload on the single functional ventricle.

The bidirectional cavopulmonary shunt has evolved into an essential intermediate step in the multistage surgical reconstruction of UVH pathologies. By early reduction of volume load on the single ventricle, preoperative conditions are optimized for the third and last procedure. After partially separating the pulmonary and systemic circulation during BCPS, the patient's vascular system is better prepared for total separation. Thus, more patients qualify for the Fontan operation, where excellent results were reported at DHM (Ono, Kasnar-Samprec et al. 2016).

The primary objective of this study is to determine survival and Fontan completion rates after stage II procedure for patients with different UVH pathologies. The secondary objective is to identify risk factors associated with unsuccessful Fontan completion.

The results of this study would allow for a more selective indication process before Fontan operation. Patients with a higher risk of unsuccessful Fontan completion could be identified and their postoperative outcomes improved by timely interventions as well as intensified monitoring.

2. METHODS

2.1. Study Design

As part of this retrospective single-center study, 525 medical records of patients who underwent BCPS were analyzed. All patients who completed stage II of UVH palliation at DHM between January 1998 and December 2018 were included. This involves patients who died before stage III, patients who completed stage III, and patients who are currently waiting for Fontan completion.

2.2. Data Collection

Medical records of all patients who were included in this study were obtained from the institutional database. In-hospital medical records as well as outpatient follow-up protocols by pediatric cardiologists were analyzed. Some patients originate from other European countries, hence follow-up examinations were typically conducted in their home countries. External follow-up reports were added to the institutional Fontan database.
To evaluate risk factors for failure to successfully achieve Fontan completion, demographics, cardiac morphology, palliative surgeries, and the postoperative course were reviewed.

2.2.1. Baseline Characteristics

Baseline patient characteristics and demographic parameters including gender, age, weight, and height at BCPS were abstracted from the medical records.
Primary diagnosis as well as associated cardiac anomalies were analyzed for each patient.

2.2.2. Preoperative Diagnostics

Echocardiography

Echocardiographic assessments from the most recent transthoracic echocardiography (TTE) report before BCPS were evaluated. Standard two-dimensional echocardiography was performed by an experienced cardiologist at DHM. TTE was used to assess ventricular function (VF) and the degree of atrioventricular valve regurgitation. Ejection fraction was

calculated, with a percentage below 50 indicating reduced ventricular function. AVV regurgitation was evaluated with color Doppler echocardiography. By measuring the jet volume, the regurgitation extent was graded. Significant AVV regurgitation was defined as moderate or more.

Cardiac Catheterization

Cardiac catheterization data were abstracted from the latest catheterization report before stage II surgery. If multiple catheterizations between stage I and stage II were performed, the most recent report before BCPS was evaluated. The examination was carried out by an experienced cardiologist at DHM.

The following pressures were included:

- Right atrial pressure (RAP)
- Right ventricular pressure (RVP)
- Left atrial pressure (LAP)
- Single ventricular pressure (SVP)
- Superior vena caval pressure (SVCP)
- Inferior vena caval pressure (IVCP)
- Aortal (proximal/ middle / distal) pressure (AoP)
- Pulmonary artery pressure (PAP)

Venous oxygen saturation in the SVC, arterial saturation in the aorta as well as the transpulmonary gradient (TPG) were also included in the data collection.

2.2.3. Perioperative Parameters

Relevant surgical data were acquired from stage II operative reports. Depending on the underlying cardiac anomaly, unilateral or bilateral BCPS was performed.

The use of extracorporal circulation, aortic cross-clamp time, type of BCPS, lowest temperature during the operation, and concomitant procedures were reviewed. Additional procedures during stage II included AVV procedure, pulmonary artery augmentation, patch aortoplasty, DKS procedure, and atrial septectomy (ASE).

2.2.4. Postoperative Period

The postoperative hospital stay and post-discharge course were evaluated. Hospital and outpatient medical records by the patients' pediatricians were reviewed.

In-hospital Postoperative Period

The postoperative course was documented in the ICU transfer protocols, the ward reports, and the discharge reports.

The following data were abstracted from the records:

- intubation period (days)
- length of ICU stay (days)
- length of hospital stay (days)
- postoperative complications
- reintubation, reoperations, reinterventions
- discharge report: EKG, SO2, VF, and AVVR

Postoperative complications involved arrhythmia, thromboembolism, pleural effusion, and diaphragm paralysis. Patients at risk or patients with signs of thrombus formation received postoperative PA angiography and echocardiography. Thromboprophylaxis management was analyzed for each patient. Reoperations and reinterventions during the hospital stay were abstracted from electronic patient charts. Early and late mortality rates were analyzed. Early death was defined as death within 30 days after surgery. Mortality between stage II and stage II was defined as late death if it occurred more than 30 days postoperatively.

Postoperative Anticoagulation Management

After stage II procedure, all patients received standard postoperative pharmacologic thromboprophylaxis. Unfractionated heparin (UFH; 50000 IU/m^2/day) was administered via intravenous injection until all central lines were removed. Partial thromboplastin time (PTT) was used to measure the response to the anticoagulation therapy and was targeted at 60 seconds. Patients with bilateral BCPS or previous thromboembolism were given additional acetylsalicylic acid or warfarin.

Postoperative examinations

All patients were examined consistently and tracked with the institutional Fontan database system. Postoperative echocardiography was performed regularly to evaluate changes in

ventricular and AVV function. The bidirectional cavopulmonary shunt was examined, along with other relevant cardiac structures. TTE was performed every day during the ICU stay. Patients with suspected thrombus formation received additional pulmonary artery angiography. Any echogenic mass within the heart, shunt or great arteries was considered a potential thrombus formation.

Post-discharge follow-up

After discharge, all patients continued follow-up by pediatric cardiologists in an outpatient setting. Relevant data were documented using the electronic patient chart of the institutional Fontan database system. The total follow-up time was calculated as the time between stage II operation and the last documented stationary or outpatient follow-up examination. Mortality cases were tracked by direct correspondence with the families and pediatricians.

2.3. Statistical Analysis

Abstracted data from the medical records were recorded in an Excel file and analyzed using the program Statistical Package for the Social Sciences (SPSS) Statistics 25.0 for Windows (IBM, Armonk, NY, USA) and R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

The patients' characteristics were reported using descriptive variables. Absolute numbers and percentages were used to express categorical data. Associations between categorical variables were drawn using the Chi-squared test.

Continuous data were expressed as mean value and standard deviation for normal distributions as well as the median and interquartile range (IQR) for non-normal distributions. Mean values of normally distributed variables were examined for significant differences using the independent student's t-test, while the non-parametric Mann-Whitney-U-test differentiated non-normally distributed variables.

Overall survival was analyzed using the Kaplan-Meier method. Fontan completion rate, mortality rate, and survival rate without Fontan completion were measured using competitive incidence analysis. At 3 and 5 years, the competing events were outlined as cumulative incidences.

Risk factor analysis

Univariate and multivariate risk models were used to determine whether certain factors are at increased risk for failure to achieve Fontan completion.

Failure to successful Fontan completion was defined as death or heart transplantation before and shortly after TCPC. Risk factors included primary diagnosis, morphological characteristics, pre-, peri-, and postoperative variables.

Univariate analysis was used to determine factors with increased risk of unsuccessful Fontan completion. Cox regression was used for multivariate analysis and examined correlations between variables and independent relationships. Statistically significant factors from the univariate analysis were discussed in the multivariate model to determine independent significance. A p-value below 0.05 was defined as statistically significant. For all independent risk factors, the cumulative incidences of Fontan completion and death after stage II were estimated.

Thrombus Formation

As the most common postoperative complication, thrombus formation and its effect on mortality were analyzed separately. Pre-, peri-, and postoperative variables of patients who developed thrombus (T+) were compared to patients who did not (T-).

Kaplan-Meier method was used to analyze overall postoperative survival. Survival times of the two groups were compared using the log-rank test. Competing risk analysis was used to estimate the cumulative incidence of Fontan completion. Gray test was used to estimate and compare the cumulative incidence function between T+ and T- groups.

3. RESULTS

3.1. Cohort

During the observation period of twenty years, 525 patients with functional UVH underwent stage II palliation at DHM (*Figure 12*). Follow-up time ranged from 1.5 to 8.7 years, with a median period of 3.4 years after the operation.

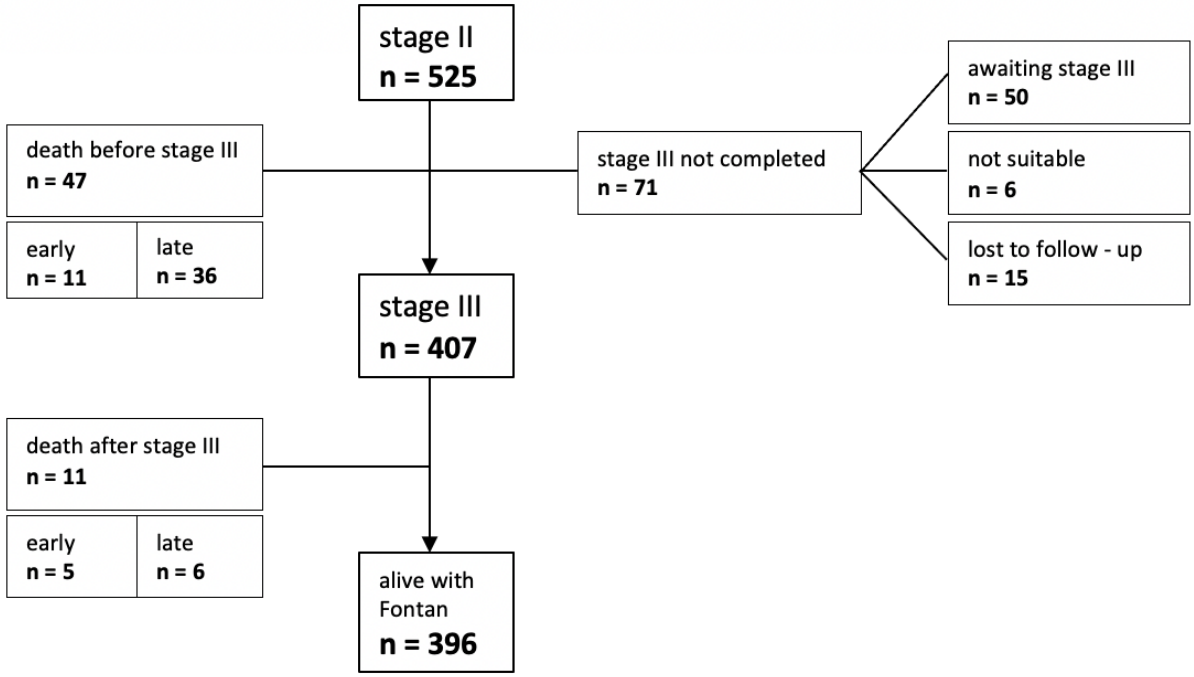


FIGURE 12. Outcomes

Among the 525 patients who underwent stage II, 407 (77.5%) completed stage III. The Fontan pathway could not be completed in 118 individuals (22.5%). Forty-seven died before Fontan circulation could be achieved. Early death occurred in 11 patients, and late death in 36.

Fifty patients are still awaiting stage III procedure, six were considered unsuitable, and 15 were lost to follow-up. Five early and six late deaths were reported of the 407 individuals who completed stage III. Of the 525 patients included in the Fontan program, 396 (75.4%) completed all three stages of UVH palliation. The median follow-up time after stage III was 4.5 years (IQR, 0.5 – 9.1).

3.2. Baseline Characteristics

Baseline demographics, primary diagnoses, and concomitant cardiac abnormalities are shown in *Table 1*. At the time of stage II operation, the median age was 4.7 months (IQR, 3.0-7.4), and the median weight was 5.6 kg (IQR, 4.7-7.4). The most frequent primary diagnosis was hypoplastic left heart syndrome, with 37% (n = 194). It was followed by univentricular heart with 17.9% (n = 94) and tricuspid atresia with 13.7% (n = 72). Double inlet left ventricle was diagnosed (n = 55) in 10.5% of the analyzed patients. Unbalanced AVSD was found in 5.7% (n = 30), followed by pulmonary atresia with intact ventricular septum (PAIVS) in 4.8% (n = 25) and ccTGA in 3.4% (n = 18) of the cohort.

Variables	***Values*** N (%) or median (IQR)
Number of patients	**525**
Age at BCPS, months	4.7 (3.0-7.4)
Weight at BCPS, kg	5.6 (4.7-7.4)
Primary diagnosis	
HLHS	194 (37)
TA	72 (13.7)
DILV	55 (10.5)
UAVSD	30 (5.7)
PAIVS	25 (4.8)
ccTGA	18 (3.4)
UVH	94 (17.9)
Other diagnoses	37 (7.0)
Associated cardiac anomaly	
TGA	145 (27.6)
DORV	58 (11.0)
CoA	72 (13.7)
Dextrocardia	45 (8.6)
Heterotaxy	36 (6.9)
Common AVV	47 (9.0)
Azygos / hemiazygos continuation	12 (2.3)

TABLE 1. Baseline Demographics and Cardiac Morphology

HLHS = hypoplastic left heart syndrome, TA = tricuspid atresia, DILV = double inlet left ventricle, UAVSD = unbalanced atrioventricular septal defect, PAIVS = pulmonary atresia with intact ventricular septum, ccTGA = congenitally corrected transposition of the great arteries, UVH = univentricular heart, TGA = transposition of the great arteries, DORV = double oulet right ventricle, CoA = coarctation of aorta, AVV = atrioventricular valve

Associated cardiac anomalies included TGA in 27.6% (n = 145) and double outlet right ventricle (DORV) in 11.0% of patients (n = 58). Coarctation of the aorta was found in 72 patients (13.7%) and dextrocardia in 45 (8.6%). Common AVV accounts for 9.0% (n = 47) and heterotaxia syndrome for 6.9% (n = 36). Azygos or hemiazygos continuation was found in 12 patients (2.3%).

3.3. Preoperative Diagnostics

Preoperative diagnostics included echocardiography and cardiac catheterization for each patient (*Table 2).* Dominant right ventricle was found in 60.0 % (n = 315) of patients and dominant left ventricle in 40.0% (n = 210). In the echocardiography report, 46 patients (8.8%) showed impaired ventricular function (VF). Significant atrioventricular valve regurgitation was observed in 59 individuals (11.2%).

Variables	***Values*** N (%), mean ±SD
Number of patients	**525**
Ventricular dominance	
Right ventricular dominance	315 (60.0)
Left ventricular dominance	210 (40.0)
Echocardiography	
Reduced VF	46 (8.8)
Atrioventricular valve regurgitation	59 (11.2)
Cardiac Catheterization	
PAP	14.8 ± 4.7
LAP	6.5 ± 2.8
TPG	8.2 ± 4.1
SV-EDP	9.0 ± 3.4
Systemic arterial oxygen saturation	75.5 ± 7.6

TABLE 2. Preoperative Diagnostics
VF = ventriular function, PAP = pulmonary artery pressure, LAP = left atrial pressure, TPG = transpulmonary gradient, SV-EDP = single ventricle end diastolic pressure

Catheterization data prior to BCPS revealed a mean PAP of 14.8 ± 4.7 mmHg and mean left atrial pressure of 6.5 ± 3.8 mmHg. Mean single ventricle end-diastolic pressure was 9.0 ± 3.4 mmHg, mean TPG was 8.2 ± 4.1 mmHg. Mean systemic arterial oxygen saturation was 75.5 ± 7.6.

3.4. Perioperative Parameters

Operative data are shown in *Table 3*. BCPS was the standard stage II procedure for all patients included in this study. Of the 525 BCPS procedures, 472 (89.9%) were performed unilaterally and 53 (10.1%) in a bilateral fashion. All patients underwent BCPS with cardiopulmonary bypass. The median duration of CPB was 63 minutes, ranging from 47 to 94 minutes. Aortic cross-clamping (ACX) during the operation was necessary in 117 (22.3%) patients with a median clamp time of 34 minutes (IQR, 22-46).

Variables	***Values*** N (%) or median (IQR)
Number of patients	**525**
Operative data	
Type of BCPS	
Unilateral BCPS	472 (89.9)
Bilateral BCPS	53 (10.1)
CPB time	63 (47-94)
Aortic cross clamp	117 (22.3)
Aortic cross clamp time	34 (22-46)
Concomitant procedure	
Pulmonary artery reconstruction	189 (36.0)
Atrioventricular valve procedure	59 (11.2)
Aorta enlargement	15 (2.9)
DKS	8 (1.5)

TABLE 3. Perioperative Parameters
BCPS = bidirectional cavopulmonary shunt, CPB = cardiopulmonary bypass, DKS = Damus-Kaye-Stansel procedure

Concomitant procedures at the time of BCPS included 189 PA reconstructions, 59 AVV procedures, 15 aorta enlargements and eight DKS operations.

3.5. Postoperative Period

Postoperative data are presented in *Table 4*. The median length of stay at the intensive care unit (ICU) following BCPS was six (IQR, 4-8) days, the median in-hospital stay was 15 days (IQR, 11-23).

Variables	***Values*** N or median (IQR)
Number of patients	**525**
Postoperative data	
ICU stay (days)	6 (4-8)
Hospital stay (days)	15 (11-23)
Reoperations with CPB	
BCPS pathway revision	14
Additional AP shunt	9
Atrioventricular valve procedure	4
Thrombectomy	4
DKS	2
Reoperation without CPB	
Pacemaker implantation	5
Diaphragm plication	4
Intervention	
Stent implantation LPA	12
Venovenous collateral coil closure	11
Balloon dilatation of LPA	5

TABLE 4. Postoperative Period
ICU = intensive care unit, CPB = cardiopulmonary bypass, BCPS = bidirectional cavopulmonary shunt, AP = aortopulmonary, DKS = Damus-Kaye-Stansel, LPA = left pulmonary artery

During the postoperative course, 42 reoperations were performed, including 33 with and nine without CPB. Reoperations after BCPS included DKS, thrombectomy, AVV procedure, AP Shunt, BCPS pathway revision, diaphragm plication, and pacemaker implantation. Procedures requiring CPB are visualized in *Figure 13*. The most common procedure was BCPS pathway revision in 14 patients, followed by additional aortopulmonary shunt in nine, AVV repair in four, thrombectomy in four, and DKS in two patients.

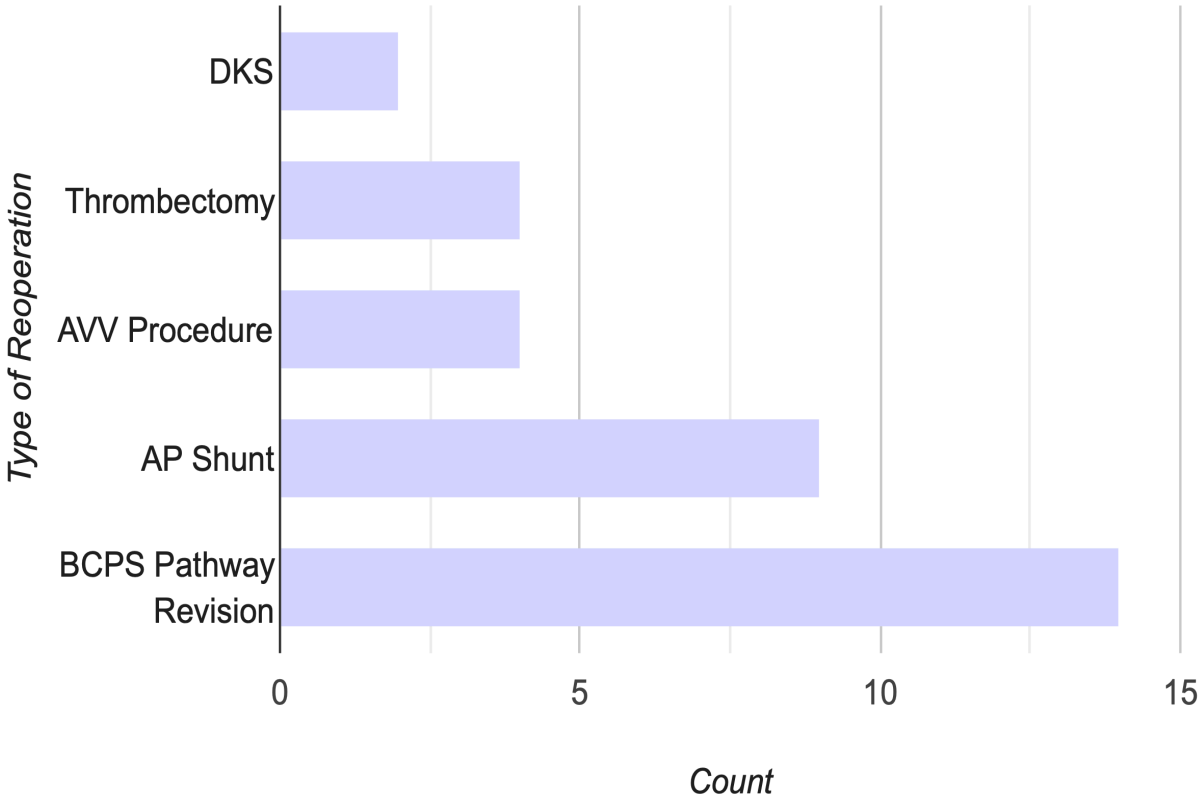


FIGURE 13. Reoperations with Cardiopulmonary Bypass
DKS = Damus-Kaye-Stansel, AVV = atrioventricular valve, AP = aortopulmonary, BCPS = bidirectional cavopulmonary shunt

Nine reoperations were performed without CPB, including five pacemaker implantations and four diaphragm plications.

Catheter interventions after BCPS included 12 LPA stent implantations, 11 coil closures of venovenous collaterals, and five LPA balloon angioplasties.

3.5.1. Complications

Severe complications, which are illustrated in *Figure 14*, were observed in 149 patients (28.4%). Since thromboembolism was the most common complication with 5.7% (n = 30), it is addressed in more detail in chapter 3.5.2.

Pleural effusion requiring drainage for more than seven days occurred in 25 patients (4.8 %), diaphragm paralysis in 24 (4.6 %), arrhythmia in 21 (4.0 %), chylothorax in 12 (2.3 %) and ascites requiring drainage in three (0.6 %).

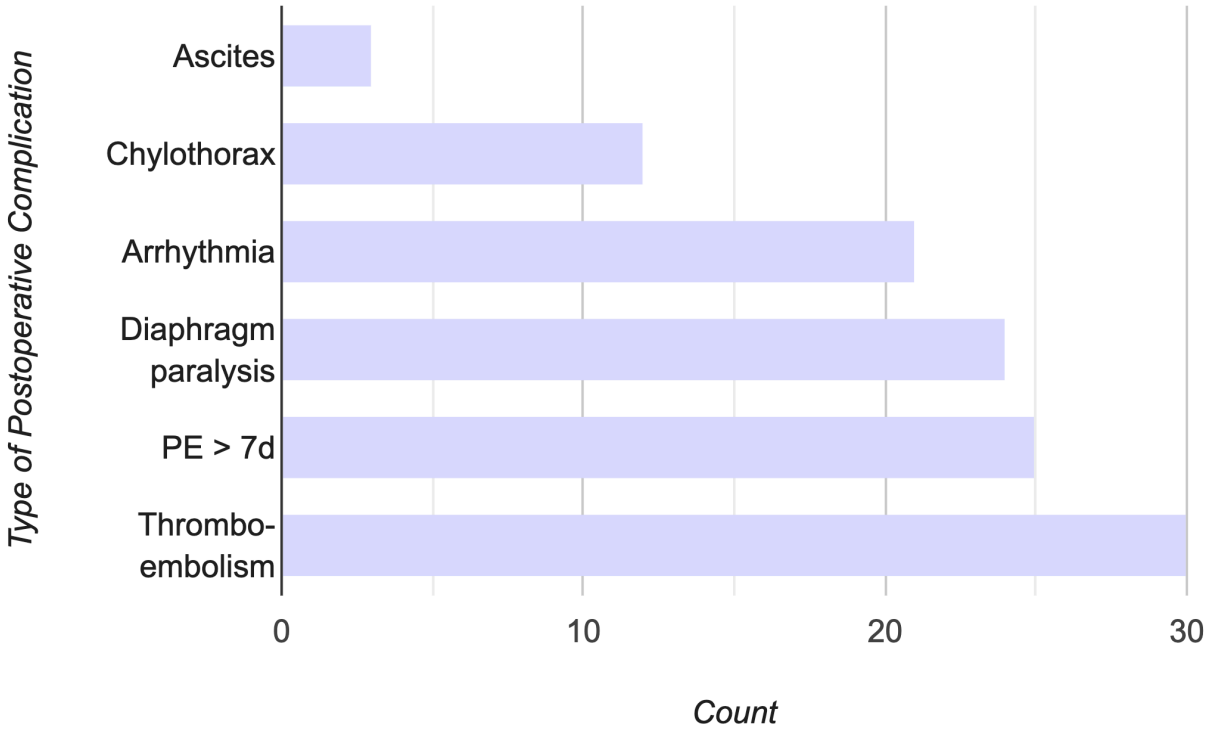


FIGURE 14. Postoperative Complications
PE = pleural effusion

Severe cyanosis after BCPS occurred in 55 patients, *Figure 15* illustrates the distribution of causes.

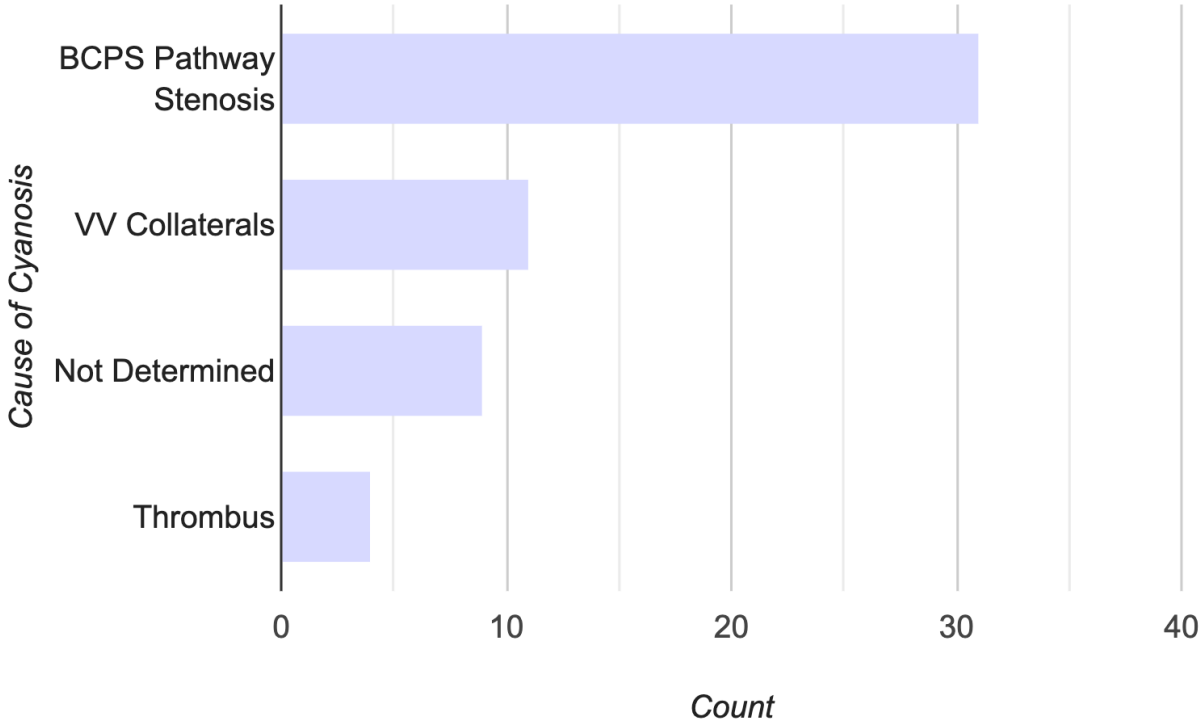


FIGURE 15. Postoperative Cyanosis
BCPS = bidirectional cavopulmonary shunt, VV= venovenous,

BCPS pathway stenosis was the cause of cyanosis in 31 patients, followed by venovenous collaterals in 11, and cavopulmonary pathway thrombus in four patients. In nine cases of cyanosis, the reason could not be determined.

Treatment for cyanosis included 14 BCPS pathway revisions, 17 catheter interventions of the BCPS pathway, four surgical thrombectomies, and 11 venovenous collateral coil closures. Nine patients, whose reason for cyanosis could not be determined, received additional systemic-to-pulmonary shunts.

Thirty-day mortality after BCPS was 2.1%. Of the nine patients requiring an AP shunt, four died after the operation. Three of 14 patients undergoing BCPS pathway revision, one of four with surgical thrombectomy, and one of 11 with venovenous coil closure died postoperatively. Extracorporeal membrane oxygenation was required in 17 (3.2 %) patients.

3.5.2. Thromboembolism

With a total of 30 patients (5.7%), thrombus formation was the most common complication among all patients undergoing BCPS. The influence of thrombus development on mortality and Fontan completion is displayed in *Table 5.*

Ten % (n = 3) of patients with thrombus (T+) experienced early death after BCPS, compared to 1.6 % (n = 8) of patients without thrombus (T-), establishing a significantly higher 30-day mortality rate (*p = 0.020*). In-hospital death was 30 % (n = 9) among the T+ group and 2.2 % (n = 11) among the T- group (*p = < 0.001*). Fontan completion rate was significantly higher in patients without thrombus compared to patients with thrombus (80.2 vs. 33.3 %; p < 0.001).

Variables	**Thrombus (+)** N (%)	**Thrombus (-)** N (%)	**p-value**
Number of patients	30	495	
Early death	3 (10.0)	8 (1.6)	**0.020**
In-hospital death	9 (30.0)	11 (2.2)	**< 0.001**
Death between stage II/ III	12 (40.0)	24 (4.9)	**< 0.001**
Fontan completion	10 (33.3)	397 (80.2)	**< 0.001**

TABLE 5. Outcomes of Patients with and without Thrombus Formation
ICU = intensive care unit, CPB = cardiopulmonary bypass, BCPS = bidirectional cavopulmonary shunt, AP = aortopulmonary, DKS = Damus-Kaye-Stansel, LPA = left pulmonary artery

Detection of Thrombus

The median time of thrombus detection was seven days postoperatively (IQR, 1-37 days). PA angiography, performed in 186 (35.0 %) patients after BCPS, detected 17 thrombi in the pulmonary artery as part of the BCPS pathway. Routinely performed postoperative echocardiography was able to identify 13 thrombi in the SVC and five in the ascending aorta. Three patients had a thrombus in the IVC, two in the atrium, and one was detected in the left ventricle. The distribution of thrombus location is visualized in *Figure 16.*

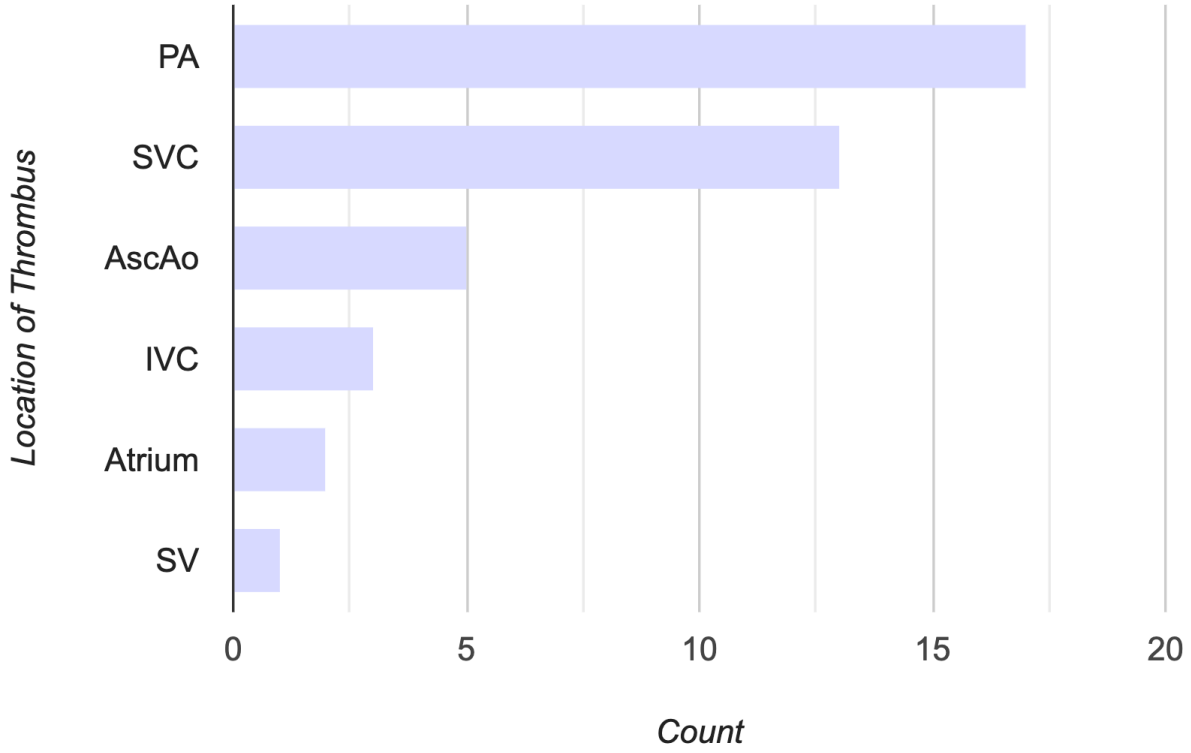


FIGURE 16. Location of Thrombus
PA = pulmonary artery, SVC = superior vena cava, AscAo = ascending aorta, IVC = inferior vena cava, SV = single ventricle

Baseline Characteristics

As shown in *Table 6*, there were no significant differences of age (p = 0.587) and weight (p = 0.225) between the two groups. Diagnosis of HLHS (46.7 vs. 36.4 %, p = 0.173), TA (10.0 vs. 13.9 %, p = 0.390), and DILV (6.7 vs. 10.7 %, p = 0.372) did not influence thrombus prevalence significantly. The only primary diagnosis associated with a significantly higher frequency of thrombus formation was unbalanced AVSD (16.7 vs 5.1 %, p = 0.022). Patients without thrombus showed a greater prevalence of associated TGA compared to those with thrombus (28.7 vs. 10.0 %, p = 0.016). Other associated anomalies listed in Table 6 did not affect the formation of thrombi significantly.

Variables	**Thrombus (+)** N (%) or median (IQR)	**Thrombus (-)** N (%) or median (IQR)	**p-value**
Number of patients	30	495	
Age at BCPS (months)	4.9 (3.1 – 7.0)	4.7 (3.0 – 7.6)	0.587
Weight at BCPS (kg)	4.9 (4.3 – 6.5)	5.6 (4.7 – 7.0)	0.225
Primary diagnosis			
HLHS	15 (46.7)	180 (36.4)	0.173
TA	3 (10.0)	69 (13.9)	0.390
DILV	2 (6.7)	53 (10.7)	0.372
UAVSD	5 (16.7)	25 (5.1)	**0.022**
PAIVS	1 (3.3)	24 (4.8)	0.575
ccTGA	1 (3.3)	17 (3.4)	0.725
Associated anomaly			
TGA	3 (10.0)	142 (28.7)	**0.016**
DORV	1 (3.3)	57 (11.5)	0.133
CoA	4 (13.3)	68 (13.7)	0.605
Dextrocardia	0 (0.0)	45 (9.1)	0.063
Heterotaxia	0 (60.0)	36 (7.3)	0.111
Azygos cont.	1 (8.3)	11 (2.2)	0.510

TABLE 6. Baseline Characteristics of Patients with and without Thrombus Formation
HLHS = hypoplastic left heart syndrome, TA = tricuspid atresia, DILV = double inlet left ventricle, UAVSD = unbalanced atrioventricular septal defect, PAIVS = pulmonary atresia with intact ventricular septum, ccTGA = congenitally corrected transposition of the great arteries, DORV = double outlet right ventricle, CoA = coarctation of aorta

Preoperative Diagnostics

Echocardiographic data showed that 23.0 % (n = 7) of patients with thrombus presented with impaired ventricular function, as opposed to 7.9 % (n = 39) of patients without thrombus (p = 0.011). Apart from ventricular EDP no significant differences were found in the catheterization reports. Patients with thrombus formation showed higher end diastolic pressure than those without (10.7 vs. 8.9, p = 0.047).

The coagulation profile between the groups showed no significant differences. Hemoglobin (g/L), platelet count (G/L), PTT (partial thromboplastin time, sec), INR (International Normalized Ratio) and fibrinogen (mg/dl) were analyzed.

Variables	**Thrombus (+)** N (%) or mean ± SD	**Thrombus (-)** N (%) or mean ± SD	**p-value**
Echocardiography			
Dominant RV	18 (60.0)	297 (60.0)	0.572
Reduced VF	7 (23.3)	39 (7.9)	**0.011**
AVVR	6 (20.0)	53 (10.7)	0.107
Catheterization			
PAP (mmHg)	16.1 ± 6.2	14.7 ± 4.6	0.261
LAP (mmHg)	7.8 ± 3.8	6.4 ± 2.7	0.109
TPG (mmHg)	6.7 ± 4.5	8.2 ± 4.1	0.138
SVP (mmHg)	82.3 ± 15.4	79.8 ± 14.6	0.429
SV-EDP (mmHg)	10.7 ± 4.3	8.9 ± 3.3	**0.047**
Ao-P (mmHg)	50.1 ± 7.3	50.9 ± 8.8	0.642
Ao oxygen sat. (%)	77.2 ± 7.0	75.4 ± 7.6	0.986

TABLE 7. Preoperative Diagnostics of Patients with and without Thrombus Formation
RV = right ventricle, VF = ventricular function, AVVR = atrioventricular valve regurgitation, PAP = pulmonary artery pressure, LAP = left atrial pressure, TPG = transpulmonary gradient, SVP = single ventricle pressure, SV-EDP = single ventricle end diastolic pressure, Ao-P = aorta pressure

Operative Data

Differences in operative variables are presented in *Table 8.* The type of BCPS did not significantly differ between the two groups. 90.0 % (n = 27) of patients who developed a thrombus received a unilateral shunt, compared to 90.1% (n = 446) of patients without thrombus (p = 0.641).

Variables	**Thrombus (+)** N (%) or median (IQR)	**Thrombus (-)** N (%) or median (IQR)	**p-value**
Number of patients	30	495	
Type of BCPS			
Unilateral	27 (90.0)	446 (90.1)	0.641
Bilateral	3 (10.0)	49 (9.9)	0.641
CPB time (minutes)	104 (60-129)	63 (43-91)	**0.025**
AXC	11 (36.7)	106 (21.4)	**0.048**
AXC time (minutes)	39 (26-64)	34 (21-45)	0.058
Concomitant procedure			
PA reconstruction	11 (36.7)	178 (36.0)	0.540
AVV procedure	6 (20.0)	53 (10.7)	0.107
Aorta enlargement	2 (6.7)	13 (2.6)	0.209
DKS	2 (6.7)	7 (1.2)	0.071
Antegrade flow open	5 (16.7)	16 (3.2)	**<0.001**
Any concomitant procedure	18 (60.0.)	271 (54.7)	0.357

TABLE 8. Operative Variables of Patients with and without Thrombus Formation
AXC = aorta cross clamping, PA = pulmonary artery, AVV = atrioventricular valve, DKS = Damus-Kaye-Stansel

The duration of CBP was significantly longer in the T+ cohort. Patients with thrombus formation had a median CPB time of 104 minutes (IQR, 60-129), compared to a median of 63 minutes (IQR, 43-91) in the T- cohort (p = 0.025). Aortic cross clamping was required more frequently during BCPS in patients who developed a thrombus postoperatively. The aorta of 11 patients (36.7 %) who developed a thrombus was clamped during surgery, in contrast to 106 (21.4%) without thrombus formation (P = 0.048). The AXC time did not differ significantly between the groups (39 vs. 34 min, p = 0.058).

No significant differences were observed regarding concomitant procedures at the time of BCPS. Patients with postoperative thrombus formation had a significantly higher rate of open antegrade flow during the operation (p < 0.001).

Early outcomes and postoperative complications

The effects of thrombus formation on the postoperative course is shown in *Table 9.*

Variables	**Thrombus (+)** N (%) or median (IQR)	**Thrombus (-)** N (%) or median (IQR)	**p-value**
Number of patients	30	495	
ICU stay (days)	18 (9-31)	6 (4-8)	**0.020**
Hospital stay (days)	39 (27-55)	15 (11-22)	**0.002**
Intervention	7 (23.3)	21 (4.2)	**<0.001**
ECMO implantation	9 (30.0)	8 (1.6)	**<0.001**
Complications			
Pleural effusion	5 (16.7)	20 (4.0)	**0.010**
Diaphragm paralysis	4 (13.3)	20 (4.0)	**0.041**
Arrhythmia	3 (10.0)	18 (3.6)	0.111
Chylothorax	3 (10.0)	9 (1.8)	**0.026**
Ascites	1 (2.3)	2 (0.4)	0.162

TABLE 9. Postoperative Course of Patients with and without Thrombus Formation
ICU = intensive care unit, ECMO = extracorporeal membrane oxygenation

Patients with thrombus formation had a significantly longer ICU stay (p = 0.020) and a significantly longer total hospital stay (p = 0.002). They stayed at the ICU for a median of 18 days (IQR, 9 – 31) and were discharged at a median of 39 days after the operation (IQR, 27-55). Patients without postoperative thrombotic complications stayed at the ICU for a median of 6 days (IQR, 4-8), and the median hospital stay was 15 days (IQR, 11-22).
ECMO was implanted with a significantly higher frequency in thrombotic patients (p < 0.001). Thirty percent (n = 9) of patients with thrombus had to be supported with extracorporal membrane oxygenation, compared to 1.6 % of patients (n = 8) without thrombus. The number of interventions after BCPS was significantly higher in the T+ group, with 23.3 % (n = 7) of patients requiring postoperative catheterizations (p < 0.001).

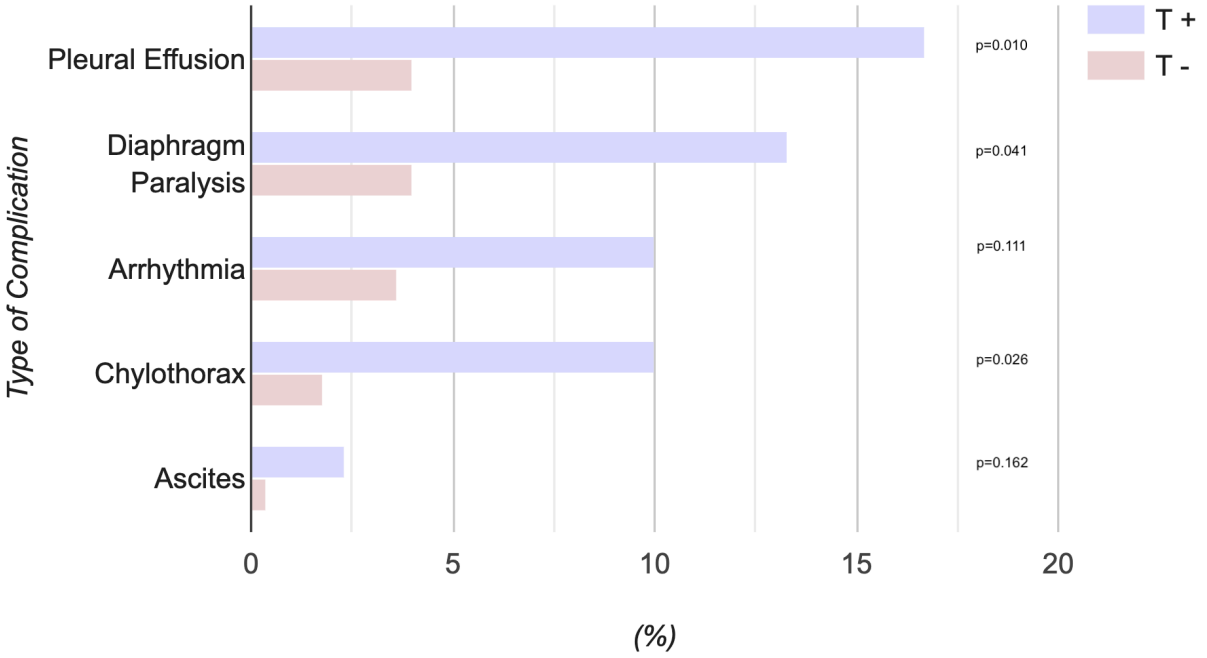


FIGURE 17. Postoperative Complications of Patients with and without Thrombus Formation
T+ = thrombus formation, T- = no thrombus formation

The development of complications varied between the two groups and is demonstrated in *Figure 17.* Patients with postoperative thrombosis had a significantly higher prevalence of pleural effusion (p = 0.010), diaphragm paralysis (p = 0.041), and chylothorax (p = 0.026). Arrhythmia (p = 0.111), and ascites (p= 0.162) showed no significant difference between the two groups.

Mortality and Fontan Completion Rate

Median follow-up time was 3.7 years after hospital discharge (IQR, 1.5-8.7). Ten percent of patients in the T+ group died within 30 days after the operation, compared to 1.6% in the T- group (p = 0.020). Among all patients who developed a thrombus, 30.0% died during the hospital stay, compared to 2.2% of patients without postoperative thrombus formation (p<0.001).

Variables	**Thrombus (+)** N (%) or mean ± SD	**Thrombus (-)** N (%) or mean ± SD	**p-value**
Number of patients	30	495	
Mortality			
Early death	3 (10.0)	8 (1.6)	**0.020**
In-hospital death	9 (30.0)	11 (2.2)	**<0.001**
Interstage Death	12 (40.0)	24 (4.9)	**<0.001**
Fontan completion	10 (33.3)	397 (80.2)	**<0.001**

TABLE 10. Mortality and Fontan Completion of Patients with and without Thrombus Formation

Survival after hospital discharge is illustrated in *Figure 18*. After one year, the estimated survival rate between patients with and without thrombus formation differed significantly (p < 0.001). One year after hospital discharge, 84.4 % (95 CI, 76.1-92.7%) of patients with thrombus were estimated to be alive, compared to 96.8 % (95%CI, 96-97.6%) of patients without thrombus formation.

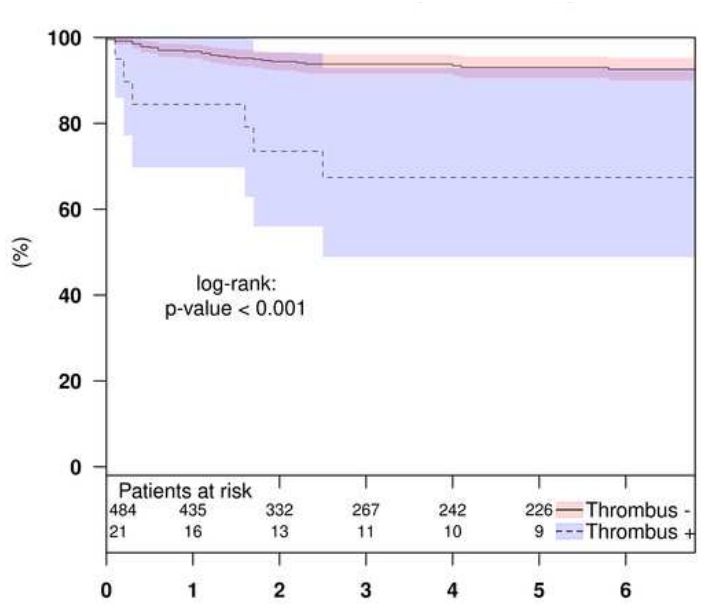


FIGURE 18. Survival of Patients with and without Thrombus Formation

Between BCPS and TCPC, 36 patients died. This involved 12 (40.0 %) patients with thrombus and 24 (4.9%) patients without, resulting in significantly greater interstage mortality for thrombotic individuals ($p < 0.001$).

After completing the second stage operation, the median interstage period before undergoing Fontan procedure was 1.6 (IQR,1.2-2.0) years. Of the 525 patients who underwent BCPS, 423 were admitted to the last stage of UVH palliation. This included 11 patients with thrombotic events after BCPS and 412 patients without.

As illustrated in *Figure 19*, the cumulative incidence of Fontan completion differed between the two groups. Patients with thrombus formation had a three-year Fontan completion rate of 52.8 % (95% CI, 30.3-75.2%). With 90.1 % (95% CI, 87.2-92.9%) Fontan circulation could be achieved with greater frequency in individuals without thrombotic events after BCPS ($p = 0.004$).

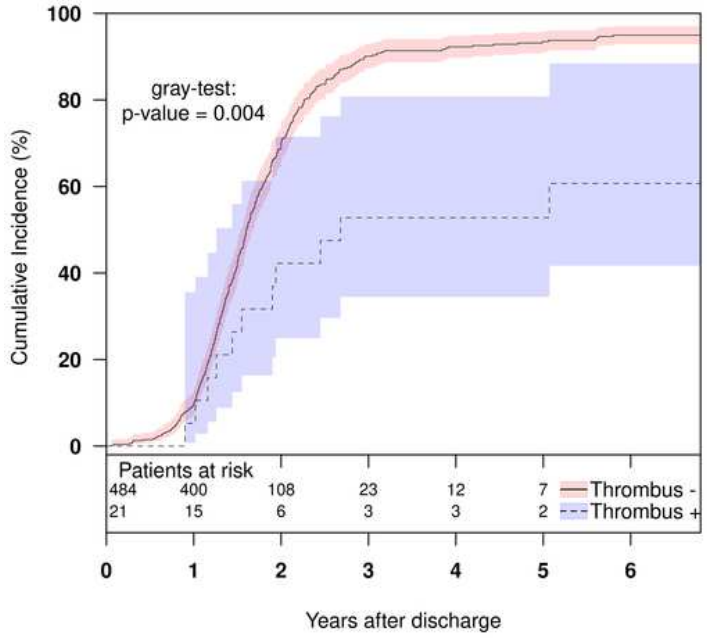


FIGURE 19. Fontan Completion Rate of Patients with and without Thrombus Formation

Risk Factor Analysis

Risk factors for thrombus formation were evaluated and are shown in *Table 11.* Uni- and multivariate logistic regression models identified morphologic, echocardiographic, and operative variables as significant risk factors.

	Univariate			Multivariate		
	OR	(95% CI)	p-value	OR	(95% CI)	p-value
UAVSD	3.76	1.33-10.65	**0.013**			
LAP	1.15	1.01-1.30	**0.029**	1.17	1.02-1.34	**0.029**
EDP	1.16	1.04-1.29	**0.009**			
Reduced VF	3.56	1.44-8.81	**0.006**			
Long CPB Time	1.36	1.11-1.66	**0.0003**	1.45	1.15-1.82	**0.002**
Concomitant DKS	5.82	1.12-30.16	**0.036**			

TABLE 11. Mortality and Fontan Completion of Patients with and without Thrombus Formation

UAVSD = unbalanced atrioventricular septal defect, LAP = left atrial pressure, VF = ventricular function, EDP = end diastolic pressure, CPB = cardiopulmonary bypass, DKS = Damus-Kaye-Stansel

Univariate analysis revealed that UAVSD was significantly associated with thrombus formation after BCPS (OR = 3.76; p = 0.013). Other cardiac malformations, such as HLHS (OR= 1.53; p = 0.259), TA (OR = 0.69; p = 0.545), DILV (OR = 0.60; p = 0.488), and bilateral SVC (OR = 0.99, p = 0.986) were not identified as risk factors in the univariate model.

Echocardiographic variables associated with a significantly increased rate of thrombus formation were LAP (OR = 1.150; p = 0.029), EDP (OR = 1.155; p = 0.009) and impaired ventricular function (OR = 3.559; p = 0.006).

Cardiopulmonary bypass time of more than 30 minutes (OR = 1.014; p < 0.001) and concomitant DKS procedure (OR = 5.821; p = 0.036) were identified as perioperative risk factors in the univariate model. An association between thrombus development and other procedures performed during stage II was not observed.

Multivariate analysis confirmed a significant association between thrombus development and long CPB time (OR = 1.013, p = 0.001) and increased LAP (OR = 1.17, p = 0.029). Other risk factors identified in the univariate model could not be confirmed in the multivariate model.

3.6. Outcomes

Cumulative incidences of Fontan completion, death and awaiting stage III at 3 and 5 years after BCPS are summarized in *Table 12.*

At three years, 83.9% have completed Fontan, 10.4% have died, and 5.7% are alive and waiting for Fontan completion. At five years, the cumulative incidences are 87.1% for Fontan completion, 10.7% for death, and 2.2% for patients awaiting stage III.

	3 years	**5 years**
Fontan completion	83.9%	87.1%
Death	10.4%	10.7%
Awaiting Fontan	5.7%	2.2%

TABLE 12. Outcomes after BCPS

The cumulative incidence of mortality, Fontan completion, and awaiting Fontan is further illustrated in *Figure 20*. The red curve shows the cumulative incidence of Fontan completion. Alive and awaiting stage III is visualized by the grey curve and mortality by the blue curve.

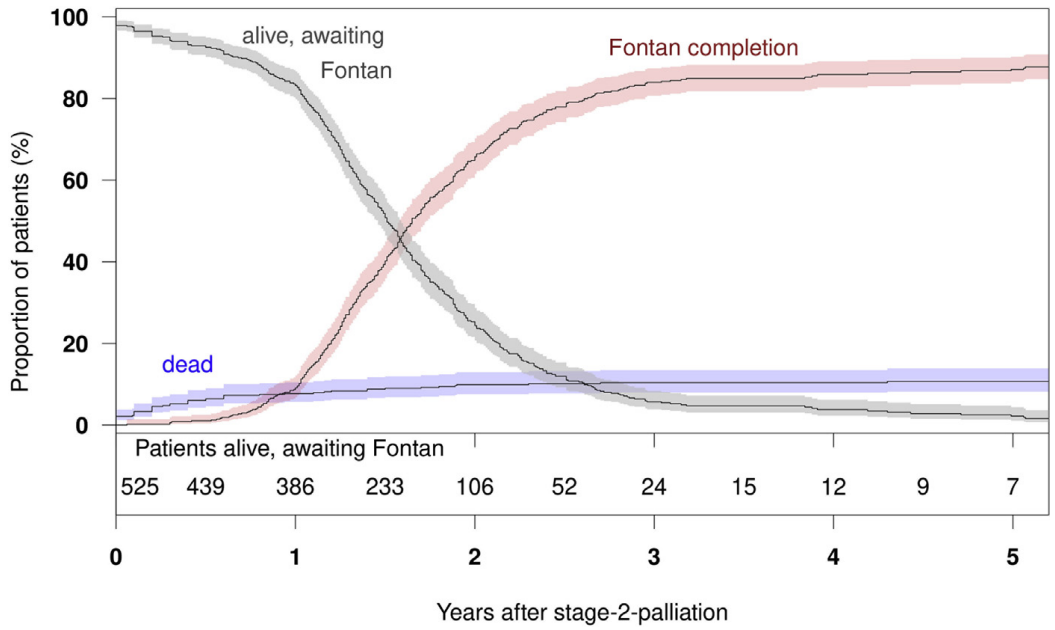


FIGURE 20. Outcomes after BCPS

3.7. Risk Factor Analysis

The following morphologic, echocardiographic, angiographic, and operative variables were identified as risk factors for failure to successful Fontan completion in uni- and multivariate risk models (*Table 13*).

Variables	**Univariate Model**		**Multivariate Model**	
	p-Value	HR (95% CI)	p-Value	HR (96% CI)
HLHS	0.016	1.9 (1.1-3.2)	**0.001**	4.1 (1.8-9.3)
UAVSD	<0.001	5.4 (2.8-10.3)	**<0.001**	10.1 (3.8-27)
Dominant RV	0.027	2.0 (1.1-3.8)		
AVV procedure	0.001	2.8 (1.6-5.1)		
Mean PAP (per mmHg)	0.005	1.1 (1.1-1.2)	**0.040**	1.1 (1.0-1.2)
Mean LAP (per mmHg)	0.001	1.2 (1.1-1.3)		
EDP	<0.001	1.1 (1.1-1.2)		
Reduced VF	<0.001	4.3 (2.2-8.4)	**0.001**	4 (1.8-9.7)

TABLE 13. Risk Factors for Failure to Successful Fontan Completion

Morphologic variables associated with unsuccessful Fontan completion in the univariate analysis were HLHS (HR = 1.9; p = 0.016) and UAVSD (HR = 5.4; p < 0.001). Other primary diagnoses of patients who underwent BCPS were not identified as risk factors. Dominant right ventricle (HR = 2.0; p = 0.027), AVV procedure (HR = 2.8, p = 0.001), elevated mean LAP (HR = 1.2; p = 0.001), elevated EDP (HR = 1.1; p < 0.001), and reduced VF (HR = 4.3; p = 0.001) were further identified as significant predictors for unsuccessful Fontan completion. Bilateral BCPS did not significantly influence Fontan completion rates (HR = 1.1; p = 0.772).

The multivariate model disclosed fewer significant variables. HLHS (HR = 4.1; p = 0.001) and UAVSD (HR = 10.1; p < 0.001) were confirmed as independent predictors for failure to complete stage III of the Fontan pathway. Multivariate analysis further identified elevated mean PAP (HR = 1.1; p = 0.040) and reduced ventricular function (HR = 4.3; p < 0.001) as independent risk factors.

Even though AVVR did not represent an independent risk factor in the multivariate model, patients with UAVSD showed a significantly higher rate of AVV operations. 26.7 % of

patients with UAVSD had concomitant AVV procedures, compared to 10.3% of patients without UAVSD (p = 0.006).

The cumulative incidence of Fontan completion and mortality of all variables identified as independent risk factors by the multivariate analysis are shown in the following figures.

Hypoplastic Left Heart Syndrome

The cumulative incidence of Fontan completion and mortality of individuals diagnosed with HLHS is illustrated in *Figure 21.* Patients with HLHS had lower incidence of completing all three stages of UVH palliation (p < 0.001) and higher cumulative mortality (p = 0.014) than patients with other primary diagnoses.

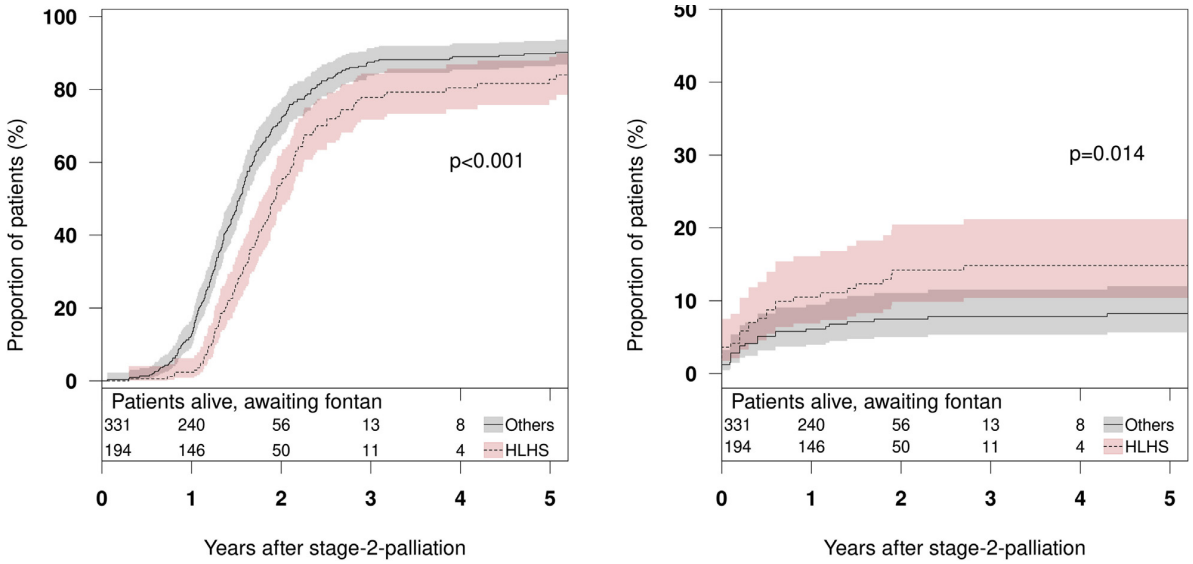


FIGURE 21. Cumulative incidence of stage III completion (left) and death after stage II of patients with HLHS (red) and patients without HLHS (grey)

Unbalanced Atrioventricular Septal Defect

Patients with UAVSD showed lower cumulative incidences of Fontan completion ($p = 0.022$) than patients with other diagnoses. Cumulative mortality was increased for patients with this cardiac anomaly ($p < 0.001$).

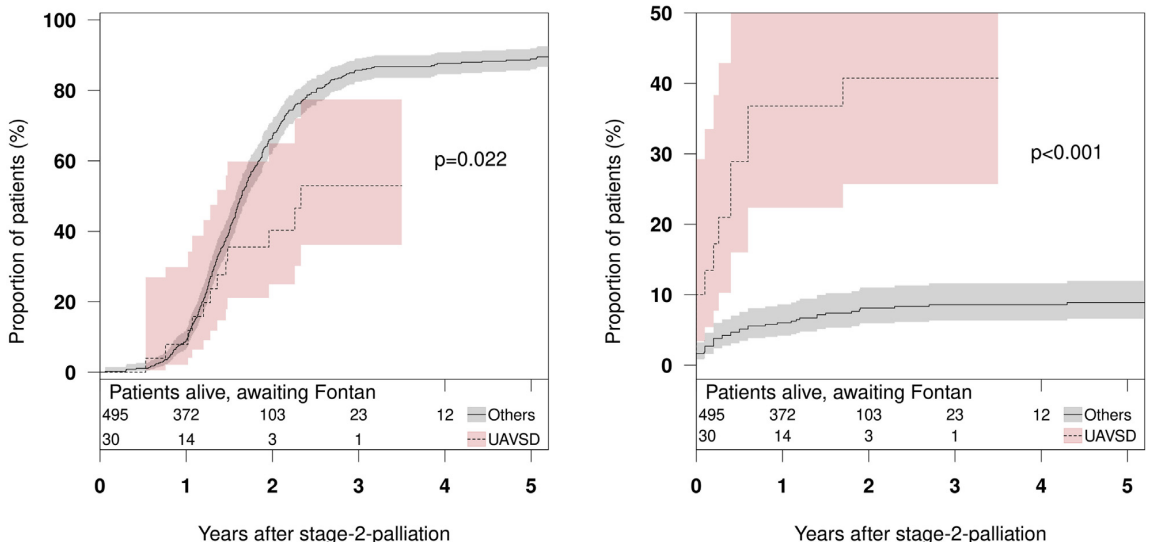


FIGURE 22. Cumulative incidence of stage III completion (left) and death after stage II of patients with UAVSD (red) and patients without UAVSD (grey)

Pulmonary Artery Pressure

Figure 23 compares the cumulative incidences of Fontan completion and cumulative mortality of patients with elevated PAP and patients without. Elevated PAP was defined as pulmonary artery pressure greater than 15 mmHg. The left graph demonstrates a lower cumulative incidence of Fontan completion for patients with PAP > 15 mmHg compared to patients with PAP < 15 mmHg (p = 0.031). The cumulative mortality of patients with PAP > 15 mmHg differed significantly from those with PAP < 15 mmHg (p = 0.017).

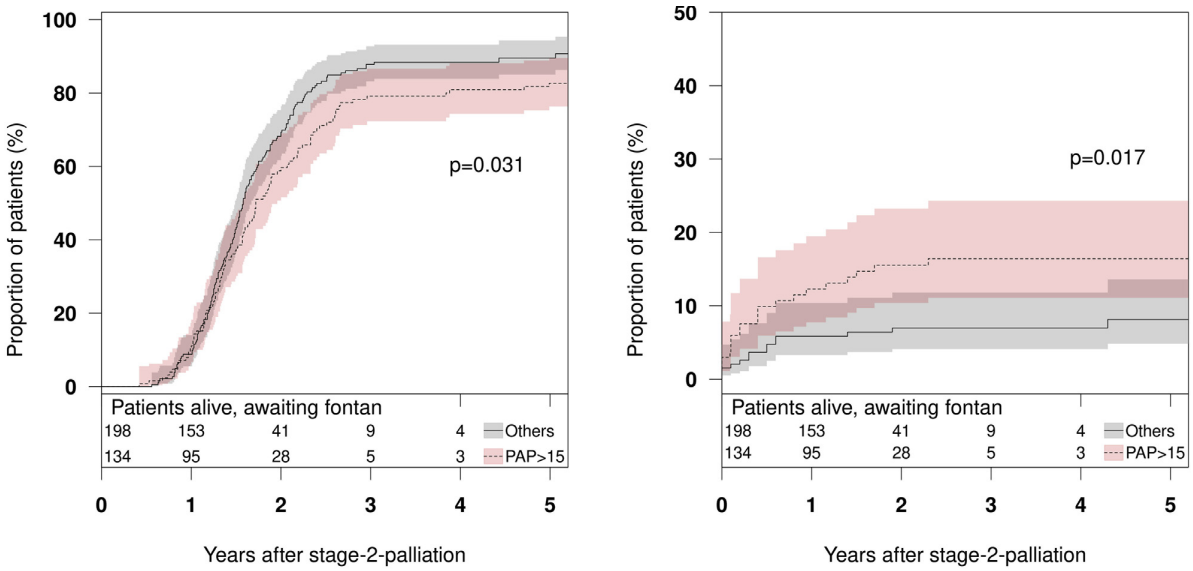


FIGURE 23. Cumulative incidence of stage III completion (left) and death after stage II of patients with PAP > 15 mmHg (red) and patients with PAP < 15 mmHg (grey)

Ventricular Function

Patients with reduced ventricular function were compared to patients with normal VF regarding the cumulative incidence of Fontan completion and mortality. Reduced VF was defined as an ejection fraction below 50 %. The left graph shows a lower incidence of Fontan completion in patients with reduced VF than those with normal VF ($p = 0.005$). As visualized in the right graph, patients with reduced VF showed higher cumulative mortality than patients without ($p < 0.001$).

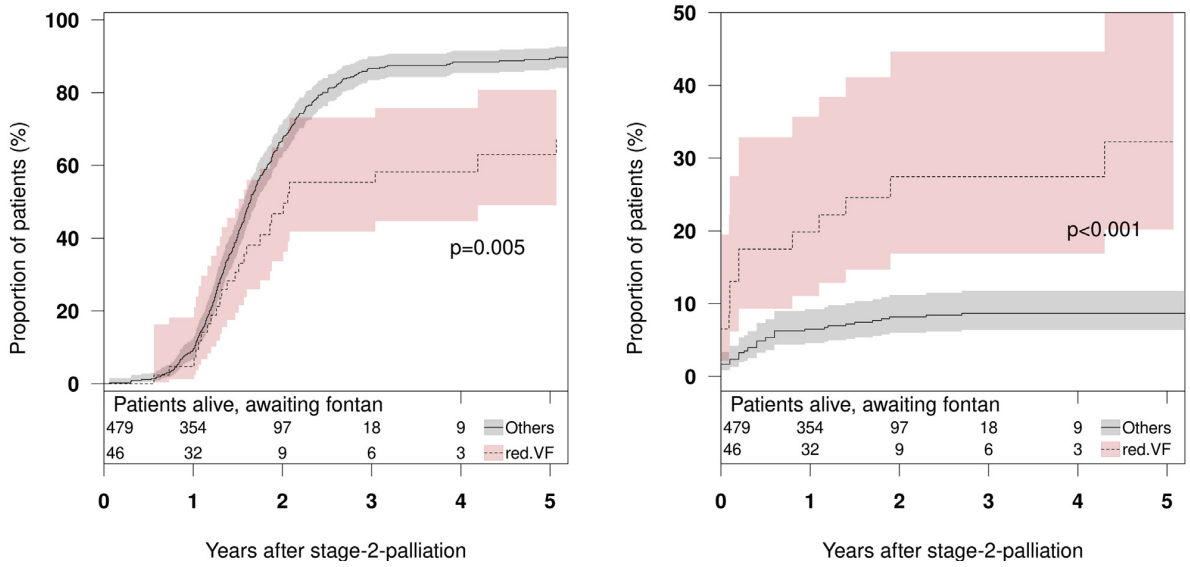


FIGURE 24. Cumulative incidence of stage III completion (left) and death after stage II of patients with reduced VF (red) and patients with normal VF (grey)

4. DISCUSSION

4.1. Mortality

The results of this study suggest that BCPS can be accomplished with relatively low perioperative and interstage mortality.

Early mortality in the present study was 2.1 %. This compares favorably to similar studies investigating short and mid-term outcomes of stage II procedures, where early mortality rates of around 5% were reported (Alsoufi, Manlhiot et al. 2012), (Lee, Aiyagari et al. 2012). Alsoufi et al. published early mortality rates of 5 %, and Lee et al. observed a 30-day mortality rate of 4.7%, respectively. Stage II was either accomplished by BCPS only (Alsoufi, Manlhiot et al.) or by BCPS and HF procedure (Lee, Aiyagari et al. 2012).

The observed mortality rates between stage II and stage III align well with previous publications, in which interstage mortality rates between 4 and 17% were reported. Interstage attrition in the present study was 6.8%. Slightly higher interstage mortality rates were reported by Alsoufi (17%) and Lee (12.7%), while Scheurer et al. observed 4% in their cohort (Scheurer, Hill et al. 2007). The most compelling explanation for discrepancies in late mortality is inconsistent institutional policies regarding cohort, indications, surgical method, postoperative care, and observation periods.

Compared to a previous publication from DHM, perioperative and interstage mortality rates after stage II procedures have risen. Cleuziou et al. investigated the outcome of BCPS without additional pulmonary blood flow in 2008 and reported an early mortality rate of 0.0% and a late mortality rate of 1.2% (Cleuziou, Schreiber et al. 2008). These changes in peri- and postoperative mortality at DHM might be due to a broader indication range for stage II procedures in the current era. Improving surgical techniques during infancy palliation and more experience in the staged UVH palliation approach contribute to broadening the candidacy spectrum for BCPS. High-risk patients, such as infants with hypoplastic left ventricle, are more likely to be admitted to the program at present times. Whereas in the 2008 study from Cleuziou et al. 19% of patients presented HLHS as their primary diagnosis, it was the most frequent cardiac malformation in this study's cohort with 37%.

4.2. Fontan Completion Rate

Most retrospective single-center studies report Fontan completion rates of 80-90% after successful second stage (Scheurer, Hill et al. 2007, Friedman, Salvin et al. 2011, Alsoufi, Manlhiot et al. 2012, Lee, Aiyagari et al. 2012). A graphic comparison between similar studies investigating mortality and Fontan completion rates five years after stage II is shown in *Figure 25.*

In this study, the cumulative incidence of Fontan completion, death, and survival without Fontan completion was performed at three and five years. At five years post BCPS, 87.1% of patients have completed Fontan, and 10.7% have died. The results pattern is consistent with previous publications investigating Fontan completion rates after BCPS.

In the previously mentioned study from Alsoufi et al., a five-year completion rate of 78% and five-year mortality rate of 17% were reported. Although they included a smaller number of patients, the cohorts had a similar distribution of ventricular dominance (Alsoufi, Manlhiot et al. 2012). Another study with a similar patient cohort, including 194 patients at Children's Hospital Boston, reported a five-year mortality rate of 12 % and a five-year completion rate of 84% (Friedman, Salvin et al. 2011). Although differences in study populations and initial palliative surgical approaches were observed between the respective studies, five-year Fontan completion and mortality rates were similar. These results indicate favorable mid-term outcomes after BCPS with relatively high subsequent Fontan completion.

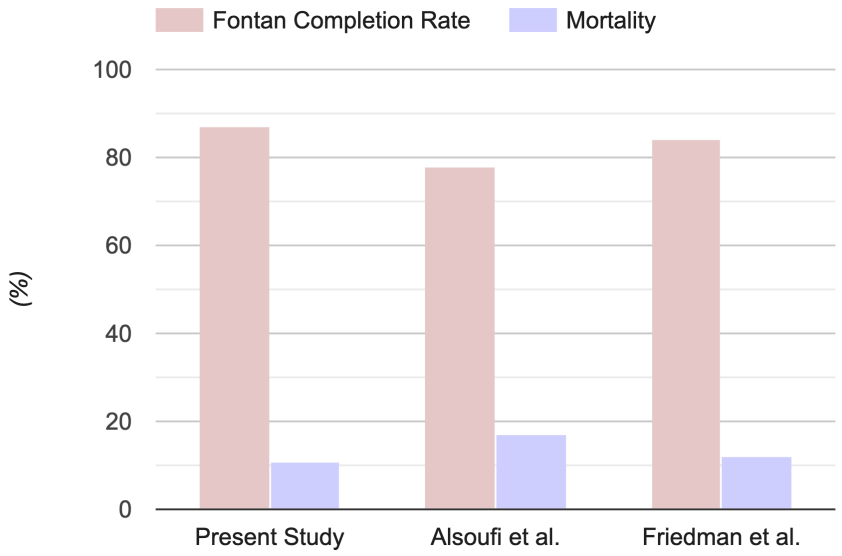


FIGURE 25. Comparison of Five-Year-Mortality Rates and Five-Year Fontan Completion Rates

4.3. Risk factors

4.3.1. Demography

In the present study, the median age was 4.7 months. Although no direct association with increased mortality was observed, several previous studies outline age at BCPS as an essential predictor for unfortunate outcome.

Friedman et al., who investigated 194 patients undergoing BCPS, reported age ≤ three months as a risk factor for failure to progress to Fontan (Friedman, Salvin et al. 2011).

This trend is supported by a different study from 2020 by Ota et al. Although there was no significant difference between patients younger and older than four months in terms of short and mid-term survival rates, patients younger than four months experienced more late deaths. (Ota, Tachibana et al. 2020)

The institutional policy at DHM favors early transitioning towards stage II pathway with consequent Fontan completion at two to four years of age. Three to six months of age is the optimal timing for BCPS, although the following arguments must be considered.

Central venous- and systemic vascular systems are not sufficiently developed in younger patients. Adequate pulmonary artery growth is of utmost importance to tolerate extreme hemodynamic changes following stage II procedure. Passive SVC-RPA flow achieved by BCPS requires decreased pulmonary vascular resistance. (Schreiber, Cleuziou et al. 2008)

On the other hand, long interstage periods after infancy palliation could increase mortality, as the hemodynamic situation after initial palliative procedures is not as stable as after BCPS (Ota, Tachibana et al. 2020). The timing of stage II is crucial for patients with HLHS and its variants, as interstage mortality after the Norwood procedure is high. Mortality rates between 10 and 25% were reported in previous studies (Hehir, Dominguez et al. 2008), (Alsoufi, Mori et al. 2015), (Ghanayem, Allen et al. 2012).

A large multicenter study by Meza et al. separated low- and intermediate- from high-risk candidates while analyzing optimal BCPS timing. Low-risk candidates with stable hemodynamic situations after Norwood showed the best outcomes if stage II was performed after three months of age. Patients with high-risk situations after initial palliation profited from earlier transition to BCPS pathway. (Meza, Hickey et al. 2018)

4.3.2. Morphology

Ventricular Dominance

The influence of ventricular dominance on Fontan outcomes remains debated. While many studies have reported RV dominance as a significant predictor for Fontan failure (Anderson, Sleeper et al. 2008), (Alsoufi, Manlhiot et al. 2012), (West, Maul et al. 2019), others have not found this association (d'Udekem, Iyengar et al. 2007), (Khairy, Fernandes et al. 2008) (Nakano, Kado et al. 2015). West et al. reported inferior results after EC-TCPC for patients with RV dominance. They associated dominant RV with higher rates of AVVR, another predictor for Fontan failure. (West, Maul et al. 2019)

Ono et al.'s previous study at DHM investigated risk factors for adverse outcomes after TCPC in a large patient cohort. Although right ventricular dominance was identified as a risk factor for a prolonged hospital stay, reinterventions after Fontan completion, and PE, it did not affect long-term outcomes. (Ono, Kasnar-Samprec et al. 2016)

While many previous authors have debated the influence of ventricular dominance on outcomes after Fontan completion, the impact on results after BCPS was less explored. Alejos et al. investigated preoperative variables of patients undergoing staged SV reconstruction. In their cohort of 129 patients, they observed that patients with dominant RV were 60 times more likely to experience failing BCPS. (Alejos, Williams et al. 1995)

Similar results were reported by Lee et al., who observed excellent results after stage II for patients with dominant LV morphology, while left ventricular hypoplasia and AVVR were predictors for worse outcome (Lee, Aiyagari et al. 2012). Consistently, Alsoufi et al. observed superior outcomes of patients with DILV and TA, compared to those with HLHS. They hypothesized that tricuspid regurgitation and right ventricular insufficiency under high pressure and immense volume loads might be the reason for poorer outcomes among patients with RV dominance. (Alsoufi, Manlhiot et al. 2012)

This pattern of previous research is quite consistent with the results of this study, where RV dominance was associated with lower rates of Fontan completion. Substantial differences between ventricular morphology, AV valves, and coronary supply of the right- and left heart may contribute to inferior outcomes for RV-dominant patients.

After SV reconstruction, the entire systemic volume load is supported by a single ventricle. Patients with dominant right ventricle lack a functional mitral valve and functional left ventricle. The morphologic right AV valve must endure higher pressures and increased volume load following UVH palliation, thus it is more likely to regurgitate. (Alsoufi, Sinha et

al. 2018) AVVR regurgitation was identified as a risk factor for adverse outcome in this study and is further discussed in chapter 4.3.3.
HLHS with systemic outflow obstruction and left ventricular hypoplasia is a typical malformation with RV dominance. The right ventricle and tricuspid valve endure high pressures and volume loads following Fontan palliation. HLHS was associated with poorer outcomes after BCPS, and lower Fontan completion rates in the present study and is discussed in more detail in the following chapter.
These considerations are of utmost importance since the population of patients with RV dominance continues to grow for UVH reconstruction. After years of gathering experience, many centers have expanded the spectrum of cardiac malformations, including more complex CHDs with right ventricular dominance.

Hypoplastic Left Heart Syndrome

The most frequent cardiac malformation in this cohort was hypoplastic left heart syndrome. Patients with HLHS typically undergo Norwood procedure as initial palliation, consisting of conduit implantation, neo-construction of the aorta, and atrioseptectomy. As mentioned previously, the interstage period before BCPS is at increased risk for mortality. The unstable hemodynamic situation following Norwood operation promotes adverse events.
After successful stage I procedure, BCPS is performed. The hemodynamic situation after stage II is considered more stable. Nevertheless, past research revealed a higher mortality risk after BCPS for this patient group (Alsoufi, Manlhiot et al. 2012), (Lee, Aiyagari et al. 2012). Alsoufi et al. observed a 5- year mortality rate of over 35% for patients with HLHS, compared to 17% for the entire cohort (Alsoufi, Manlhiot et al. 2012). These findings are consistent with the present study, where the influence of HLHS on interstage mortality and Fontan completion was shown. The cumulative mortality was almost twice as high for HLHS after five years, compared to other diagnoses. HLHS was also a significant predictor for failure to complete Fontan. HLHS was associated with lower rates of Fontan completion in this cohort, compared to other CHDs. Patients with a hypoplastic left ventricle, atretic aorta, and atretic mitral valve rely on the right ventricle and tricuspid valve to support both pulmonary and systemic circulation. After Norwood and BCPS, even though the venous return is partially directed into the RPA, the right ventricle and tricuspid valve are subject to high pressures and volume overload. This might be a reason for long-term ventricular insufficiency and tricuspid valve regurgitation, resulting in a higher mortality risk and failure to progress to stage III.

Unbalanced Atrioventricular Septal Defect

The second cardiac malformation with poorer Fontan completion rates and increased mortality in this cohort was UAVSD. It was associated with the highest early mortality, with 10%, followed by HLHS, with 3.6%.

Previous research has revealed similar associations (Lee, Aiyagari et al. 2012), (Owens, Gomez-Fifer et al. 2009). They showed that patients with UAVSD are at increased risk of mortality and failure to complete Fontan due to concomitant cardiac and non-cardiac malformations. Lee et al. reported increased early mortality rates for patients with UAVSD. Within the first 30 days after stage II operation, 12.3% of patients with this anatomic malformation died. Not only did UAVSD account for the highest early mortality rate in their cohort, but they also identified this diagnosis as an independent risk factor for failure to progress to Fontan. (Lee, Aiyagari et al. 2012)

The increased number of associated anatomic and genetic defects could explain poorer outcomes for patients with UAVSD. In the present cohort, AVV regurgitation among UAVSD patients was observed in 26.7%, compared to 10.3% with different primary diagnoses. Although AVVR did not prove to be an independent risk factor in this study, many previous studies have agreed that regurgitation of the AV valve is associated with poorer outcome (Hansen, Uebing et al. 2011), (Carlo, Carberry et al. 2011), (Imai, Seo et al. 1999).

Owens et al. followed patients with UAVSD undergoing SV palliation for five years. Seventy-three percent had extracardiac abnormalities, and 30% presented with additional AVVR. Patients with concomitant AVVR were at significantly increased mortality risk during the observation period. (Owens, Gomez-Fifer et al. 2009)

Non-cardiac abnormalities associated with this CHD include genetic disorders, such as Trisomy 21 (Morlando, Bhide et al. 2017). Although Trisomy 21 was not evaluated as a risk factor in the present study, several previous studies have shown poorer results for this patient group In a US nationwide multicenter study with 23.271 patients, Allen et al. concluded that mortality after stage II and stage III procedure is significantly increased for patients with Down syndrome (Allen, Anderson et al. 2021). Gupta-Malhorta reported similar results, with a 35% mortality rate after BCPS for patients with Trisomy 21, compared to 9% for patients without this genetic disorder (Gupta-Malhotra, Larson et al. 2010).

These results demonstrate that patients with UAVSD represent a high-risk patient group that must be evaluated thoroughly before starting UVH reconstruction.

4.3.3. Echocardiography

Preoperative echocardiography was routinely performed before BCPS to assess valvular competence and ventricular function. The results of this study emphasize the importance of preoperative echocardiography in identifying potential risk factors for adverse outcomes. High-risk patients should be carefully monitored, and additional interventions during BCPS may contribute to improved outcomes.

Atrioventricular Valve Regurgitation

Volume unloading of the SV by partially separating pulmonary and systemic circulation improves ventricular remodeling. Although this association has been commonly agreed upon, the effect on atrioventricular valve regurgitation remains discussed. While some authors reported a reduction of the regurgitation degree after BCPS without concomitant valvuloplasty (Mahle, Cohen et al. 2001), others have not found this association (Yamagishi, Masuoka et al. 2014), (Kasnar-Samprec, Kuhn et al. 2012).

Yamagishi et al. investigated the AVV insufficiency degree in UVH patients before and after BCPS and concluded that volume reduction after BCPS reduces annulus dilatation of the AV valve. Although this effect could be observed, they did not notice an improvement in the regurgitation degree. (Yamagishi, Masuoka et al. 2014) Similar results were observed by Kasar-Samprec et al. at DHM. They evaluated 90 patients with HLHS undergoing BCPS and noticed a decrease in AVV size due to volume unloading, but the degree of valve regurgitation remained unchanged. (Kasnar-Samprec, Kuhn et al. 2012) These results opened discussions about the approach to address atrioventricular regurgitation at the time of BCPS in patients with significant regurgitation.

The consideration of valvuloplasty at the time of BCPS is especially relevant since early studies have reported poorer short and mid-term outcomes for patients with atrioventricular valve insufficiency. Imai and colleagues analyzed 372 SV patients undergoing Fontan procedure, 169 of whom showed various degrees of AVVR. They observed a ten-year survival rate of 81% in the AVVR group, compared to 91% in the non-AVVR group. (Imai, Seo et al. 1999)

A more recent study by Hansen et al. shows similar results for patients with AVVR undergoing BCPS. They evaluated risk factors for adverse outcomes after BCPS of patients with previous Norwood procedure. Patients with tricuspid regurgitation represented a group with significantly increased risk of adverse outcomes. Volume unloading alone after BCPS

was insufficient to improve more than moderate tricuspid regurgitation. (Hansen, Uebing et al. 2011)

In the present study, all 59 patients who showed relevant AVVR received concomitant AV valve procedure. Although AVVR was identified as a risk factor for failure to complete Fontan in the univariate analysis, it could not be verified in the multivariate model. Cumulative incidence analysis showed significant differences in Fontan completion and mortality. Patients with AVVR were at increased risk of mortality and showed significantly lower completion rates than patients without valve insufficiency.

The repair of AVV regurgitation is especially relevant, as good ventricular function is associated with valvular competence. If the AV valve closes insufficiently, the single ventricle is constantly overloaded with volume. This altered hemodynamic situation could result in ventricular remodeling, if not addressed timely.

The results of this study demonstrate that more than moderate regurgitation of the AV valve is an essential predictor for adverse outcome. Patients with significant AVVR should be monitored carefully and considered for valvuloplasty at the time of BCPS.

Impaired Ventricular Function

Patients with reduced VF represent a high-risk patient group among Fontan candidates. As discussed above, dominant right ventricle pathologies are at even greater risk of poor outcomes. Before BCPS, the single ventricle supports both pulmonary and systemic circulations. After partial cavopulmonary separation, even though the volume load on the SV is reduced, adequate VF is required to allow efficient volume ejection.

Previous studies have shown that myocardial dysfunction results in adverse postoperative outcome (d'Udekem, Xu et al. 2012), (Lee, Aiyagari et al. 2012).

Lee et al. included right and left single ventricle pathologies and identified ventricular dysfunction as a significant predictor for adverse outcome. Patients with impaired ventricular function made up 7.5% of their cohort. (Lee, Moon et al. 2018)

No relationship between ventricular dysfunction at the time of BCPS and interstage attrition was found in the single-center study by Carlos et al., where only HLHS patients were included. Although no direct association was observed, they identified more than moderate tricuspid regurgitation as a significant risk factor for mortality. They further argued that AVVR could eventually lead to progressive ventricular insufficiency, if not addressed adequately. (Carlo, Carberry et al. 2011)

In the present study, 46 patients showed reduced ventricular function in terms of ejection fraction below 50%. Myocardial dysfunction was identified as an independent predictor for interstage mortality and failure to complete Fontan in the multivariate analysis. Five years after BCPS, patients with reduced VF showed a mortality rate of 30%, compared to 5% of patients with normal ventricular function. These results demonstrate the significance of ventricular competence for successful Fontan completion. In terms of physiology, ventricular morphology and atrioventricular valve function are closely related. If the ventricle lacks adequate function, an insufficient AV valve contributes to chronic volume overload on the ventricle, resulting in deterioration of function.

A meta-analysis by d'Udekem et al. including 34 relevant publications demonstrates excellent 20-year survival rates of over 80 % after Fontan procedure. Although good results were reported, myocardial dysfunction was identified as a predictor of Fontan failure and late death. (d'Udekem, Xu et al. 2012)

Special care and intensified monitoring must be implemented to ensure short-term survival after BCPS for patients with reduced ventricular function. Impaired VF is a risk factor not only for interstage attrition, but also for long-term Fontan failure.

4.1.4. Cardiac catheterization

Pulmonary Artery Pressure

Angiographic assessment prior to stage II is routinely performed at DHM. The relevance of specific parameters on clinical outcomes is subject of discussion.

Some authors identified elevated mean pulmonary artery pressure as an indicator of adverse short and mid-term survival (Tran, Sullivan et al. 2018), (Alejos, Williams et al. 1995), while other previously mentioned authors have not found a direct association (Alsoufi, Manlhiot et al. 2012), (Lee, Aiyagari et al. 2012).

An early report from Alejos et al. showed in-hospital survival rates of 80% for patients with PAP > 18mmHg, compared to 96% for patients with regular PAP. The authors further showed that patients with elevated PAP were five times less likely to complete all three stages of the Fontan pathway. (Alejos, Williams et al. 1995)

Tran et al. analyzed the in-hospital course of patients undergoing BCPS, particularly focusing on preoperative angiographic measurements. They identified preoperative elevated PAP > 16mmHg as a predictor for early mortality. The subgroup with elevated PAP independent of

pulmonary vascular resistance had the highest in-hospital mortality rates. Increased PVR alone was not a significant risk factor. (Tran, Sullivan et al. 2018)

Other results were reported by Alsoufi and colleagues, who identified PVR > 3 Wood units as an unfavorable factor associated with failure to progress to Fontan. They argued that timely neonatal interventions could prevent high PVR and improve results regarding Fontan completion rates. (Alsoufi, Manlhiot et al. 2012)

Discrepancies in previous studies concerning PAP as a predictor for outcome may result from different stage II indications, different pre- and postoperative care regulations, and institutional preferences for stage I and stage II surgical techniques.

The current study defined PAP greater than 15 mmHg as elevated pulmonary artery pressure. Both univariate and multivariate analysis identified elevated mean PAP as a significant risk factor for failure to complete Fontan. These results may provide valuable insights for revising contraindications for BCPS.

In a study focusing on BCPS for patients with Ebstein malformation at Mayo Clinic, the authors defined the following parameters as contraindications for the procedure: PAP > 20mmHg, PVR > 4 Wood units, LVEDP or LA pressure > 12mmHg (Raju, Dearani et al. 2014).

Similar contraindications could be considered following the results of this study. Elevated PAP was associated with higher mortality rates and decreased chance to progress through the intended Fontan stages. One interpretation might be that blood follows a certain pressure gradient when passing through the SVC-RPA connection. If the pulmonary vascular system pressure increases, central venous pressure adapts by rising concomitantly to provide adequate flow through the connection. Severe complications, such as pleural effusions, follow these pressure changes, as increased hydrostatic pressure results in transudative effusions (Krishna and Rudrappa 2022). These associations must be considered, given that PE is the second most prevalent complication in this study's cohort. Timely interventions focusing on lowering PAP in high-risk patients might contribute to improving outcomes after BCPS.

4.4. Thromboembolism

The results of this study highlight the relevance of thromboembolism as a severe complication following BCPS. Although other stages of SV palliation are at even greater risk of thrombus formation due to the implantation of prosthetic shunt material, this postoperative issue remains an underlying risk for adverse outcome after stage II procedure.
Previous studies have shown varying rates of thrombus development in the interstage period, ranging from 0 to 28% (Agarwal, Firdouse et al. 2018).
Manlhiot et al. reported that 28 % of their cohort with UVH pathologies had thrombotic events after BCPS. (Manlhiot, Brandao et al. 2012). Hansen et al., who analyzed patients with HLHS undergoing BCPS and HF, observed an 8% rate of thrombus development (Hansen, Uebing et al. 2011). Discrepancies in patient cohorts, diagnostic imaging methods, postoperative anticoagulation regimens, and surgical techniques may explain the variety of thrombus observations. The current study presents a large cohort with 525 patients undergoing stage II. Thrombus development occurred in 5.7% after performing partial cavopulmonary anastomosis and was associated with significantly increased early, in-hospital, and interstage mortality, as well as less likelihood of successful Fontan conversion. ICU stay, total hospital stay, reintervention rate, and postoperative complication events were significantly higher for patients who developed thrombus. Therefore, the discussion of pathophysiology, risk factors for thrombus development as well as consistent thromboprophylaxis management could contribute to improving outcomes of this high-risk patient group.

Pathophysiology

Virchow's triad identifies three factors promoting thromboembolic events - disturbances in blood flow, endothelial damage, and hypercoagulability (Kushner, West et al. 2021).
Stasis, turbulence, and decreased rate of PA flow caused by the low pressure of returning venous blood induce disturbances in blood flow in Fontan patients. Due to the absence of a sub-pulmonary ventricle after BCPS, the venous return flows passively to the lungs through the superior cavopulmonary anastomosis. The non-pulsatile flow through the connection increases the risk of thrombus development. (Van Den Helm, Sparks et al. 2022)
Damage to the endothelium in UVH patients is caused by chronic hypoxemia and hyperviscosity (Binotto, Maeda et al. 2005). Other factors promoting endothelial damage are surgical trauma and tissue manipulation as well as placement of central venous catheters and

CPB utilization. Accurate anastomosis of the SVC and RPA is crucial to ensure laminar blood flow and prevent thrombus formation in the BCPS circuit. (Van Den Helm, Sparks et al. 2022)

Hypercoagulability is the third factor promoting thrombus formation. Some authors have observed that patients with SV pathologies experience hypercoagulable states due to diminished concentrations of antithrombotic factors, like protein C and antithrombin III (Odegard, McGowan et al. 2002), (Ravn, Hjortdal et al. 2001).

Most thrombi in this study's cohort were found in the PA, followed by SVC. Thromboembolic complications in the arterial circulation were observed less frequently, with most thrombi being detected in the ascending aorta, atria, and left ventricle. Additional explanations for arterial thromboembolism in SV patients might be atrial arrhythmias and paradoxical embolism via right-to-left shunting.

Risk Factors

Although the implantation of artificial materials is not indicated during this stage of Fontan palliation, several anatomical, physiological, and operative variables promoted thrombogenic conditions in this study. UAVSD, high preoperative LAP and EDP, impaired VF, prolonged CPB time, and concomitant DKS were identified as risk factors in the univariate model. Consistent with prior research, elevated EDP, increased atrial pressue and reduced ventricular function were preoperative risk factors encouraging thrombogenic conditions. Forbes et al. investigated patients with thrombosis in the cavopulmonary circuit and associated increased EDP, increased right atrial pressure as well as reduced VF with thromboembolic events (Forbes, Rosenthal et al. 1997).

The physiological linking of these variables in promoting thrombogenic conditions is further supported by the results of Schwartz et al. They evaluated angiographic factors associated with elevated EDP in Fontan patients and reported associations between elevated EDP and reduced VF. They argued that reduced VF as well as elevated EDP, contribute to blood stasis, which is one of the main factors promoting thrombogenic conditions. (Schwartz, Brock et al. 2018)

Another prospective study by Tzanetos confirms the hypothesis that reduced VF is associated with higher risks of thrombus formation. Patients with impaired VF show slow and non-pulsatile flow, contributing to an increased risk of thrombus formation. (Todd Tzanetos, Yu et al. 2012)

Another group with an increased risk of thrombus development was patients who required CPB for more than 30 minutes. CPB leads to disturbances of blood flow as well as platelet activation (Weerasinghe and Taylor 1998). Considering the findings of previous research that SV patients are at increased risk of hypercoagulable conditions, the issue of platelet activation becomes even more relevant (Ravn, Hjortdal et al. 2001). The increased thrombogenicity and platelet activation in patients with CHD, caused by dysfunction of the endothelium, adds to the problem (Kajimoto, Nakazawa et al. 2007). Combined with the artificial surface of CPB cannulas, which further promote plantlet adhesion and activation, unfortunate conditions for thrombus development are the consequence.
Standardized UFH is administered prior to CPB initiation to prevent clot formation. Nevertheless, thrombus formation is a common issue due to hypercoagulable states of SV patients and infantile immaturity of the coagulation system, resulting in resistance to anticoagulants (Gruenwald, Manlhiot et al. 2010).
Given the increased rate of thrombus formation of several patient groups in this study, special monitoring and individualized thromboprophylaxis protocols must be implemented to prevent this postoperative complication.

Thromboprophylaxis

The management of patients with thrombotic events remains a challenging task during the postoperative period. Despite the significantly higher mortality and major clinical implications, no consensus exists regarding the prophylaxis of this complication. Standardized thromboprophylaxis regimens after stage II remain absent, even though the American College of Chest Physicians' advocated for the routine use of postoperative UFH (Monagle, Chan et al. 2012). While some institutions prefer single admission of UFH, VKA, low-molecular-weight-heparin (LMWH), or acetylsalicylic acid (ASA), others support combination therapy. The advantage of either antiplatelet or anticoagulative treatment has yet to be demonstrated and remains actively debated. (Agarwal, Firdouse et al. 2018)
ASA serves as an inhibitor of cyclooxygenase 1, which reduces levels of thromboxane A2 and inhibits platelet aggregation. Although some centers advocate the use of ASA in the interstage period following shunt implantations, previous research shows inadequate platelet inhibition in UVH patients. (Mir, Frank et al. 2015), (Tomkiewicz-Pajak, Wojcik et al. 2015)
VKAs block the activation of coagulation factors II, VII, IX, and X as well as proteins C and S. Adequate response to VKAs is measured with the INR targeted at 2-3 in Fontan patients.

The inadequate synthesis of VKA-dependent clotting factors in patients with CHDs might impact the response. (Odegard, McGowan et al. 2002), (Ravn, Hjortdal et al. 2001)
DOACs directly bind a specific coagulation factor, in particular factor Xa and thrombin. Although the effects of DOACs in adults are promising, experience in patients with CHD is limited and a general recommendation for Fontan patients remains absent. (Pujol, Niesert et al. 2016) Heparin is another anticoagulant inactivating thrombin and factor Xa by potentiation of antithrombin. Adequate response to Heparin therapy, which is available as UFH and LMWH, is measured by the PTT. LMWH is more suitable for outpatient use and less prone to severe side effects, most notably heparin-induced thrombocytopenia, while UFH is preferred during in-hospital stay. (Heidendael, Engele et al. 2022)
In this study, all patients received standard admission of UFH (5000/ IU/m^2/day) until removal of all central lines. The target PTT was 60 seconds for patients without risk factors and 60-80 seconds for patients with reduced VF, high preoperative PAP, and postoperative hypoxemia. Later, no routine antithrombotic prophylaxis was used. Nevertheless, due to bilateral BCPS, prior thrombotic events or persistent AP shunts, some patients received ASA or warfarin postoperatively.
Comparison of different thromboprophylaxis regimens after Fontan operation have been reported by some previous authors, however considerable variability exists in the protocols used. A meta-analysis of 1200 patients demonstrated that general thromboprophylaxis after Fontan surgery was beneficial. They observed a 18.6% rate of thrombus development in patients who did not receive thromboprophylaxis, compared to 8.6% with ASA and 9% with VKA. Although no significant difference between both included agents was detected, the results suggest the clinical relevance of thromboprophylaxis in Fontan patients. (Alsaied, Alsidawi et al. 2015)
Manlhiot et al. compared different thromboprophylaxis protocols after each stage of Fontan palliation at the Hospital for Sick Children in Toronto. They analyzed single-agent ASA, enoxaparin, and warfarin, as well as the combination of ASA and enoxaparin, and no thromboprophylaxis. Single enoxaparin had the lowest rate of thrombus formation and was associated with significantly decreased thrombus formation compared to no prophylaxis. (Manlhiot, Brandao et al. 2012)
Future randomized trials are essential to compare various thromboprophylaxis options. Efforts to encourage standard protocols might benefit the postoperative course of Fontan patients suffering from this severe complication.

5. LIMITATIONS

The study is limited due to the retrospective design, resulting in the following bias. Most notably, selection bias from including only patients with BCPS operation instead of all patients who had indications for BCPS but were still waiting at that point. A second potential limitation is the inconsistency of preoperative echocardiographic and angiographic data. The examinations were performed by several cardiologists, resulting in an interobserver variability of results.

Since patients from 1998 to 2018 were included, it is notable that surgical techniques have evolved over the past 20 years, as well as postoperative intensive care. Moreover, BCPS was performed by several surgeons, which may also contribute to study limitations.

Concerning the detection of thrombus as a postoperative complication, only thrombi with clinical evidence were detected by PA angiography or echocardiography. There was no standard protocol for thrombus detection, which may have resulted in fewer reports.

6. SUMMARY

With 1-2 % of congenital heart defects, UVH is a rare but complex cardiac condition that requires interdisciplinary expertise. With high early mortality rates and poor life expectancy, the surgical treatment of these patients seemed inconceivable not long ago. After years of progress in different specialties, infants diagnosed with UVH have the prospect of a longer and quality-enhanced life. Surgical Fontan palliation with complete separation of systemic and pulmonary circulations is the primary goal for patients with UVH. Staging the process to Fontan circulation has made the hemodynamics adjustment of complete circulatory separation easier and improved results. The bidirectional cavopulmonary shunt is the necessary intermediate step before Fontan completion, as the volume load of the SV is reduced and optimal conditions for TCPC are achieved. Nevertheless, certain risk factors for adverse outcome and less likelihood of Fontan completion remain.

This study aimed to evaluate early and midterm outcomes of patients undergoing stage II palliation and identify predictors of mortality and failure to complete Fontan. For this purpose, 525 patients undergoing BCPS at DHM between 1998 and 2018 were analyzed. HLHS and UAVSD were identified as independent risk factors for adverse results after BCPS. Patients with impaired ventricular function and elevated PAP showed less chance of Fontan completion and worse results after stage II. Although AVVR was not an independent risk factor, patients with UAVSD and reduced VF at the time of BCPS showed a significantly higher prevalence of atrioventricular valve regurgitation. The most common complication after stage II surgery was thrombus formation, which adversely affected mortality and Fontan completion. Elevated left atrial pressure and long CPB time were indepenant predictors for postoperative thrombus development.

The results of this study enhance the understanding of adverse outcomes in specific patient subgroups. Although outcome after BCPS and TCPS is excellent, some patient subgroups experience increased rates of mortality and postoperative complications. Identifying these patients with increased risk of staged palliation failure, who might benefit from intensified monitoring and individualized treatment regimens, remains a continuing challenge in congenital heart surgery. Further research focusing on certain anatomic and physiologic risk factors could contribute to a broader understanding and eventually to individualized management of these patients.

Acknowledgments

Throughout my time at German Heart Center Munich, I received exceptional support on a professional and personal level. I want to use this as an opportunity to offer my sincere appreciation to several individuals involved.

Firstly, I would like to express my gratitude to Prof. Dr. Jürgen Hörer for the opportunity to conduct this dissertation under his supervision and guidance. He sparked my passion for congenital heart surgery and has supported me greatly over the past years.

Secondly, I would like to thank my mentor Prof. Dr. Masamichi Ono for his invaluable efforts in supporting and assisting my dissertation process at every stage. I am grateful for the countless talks and exciting discussions on relevant topics.

I would also like to extend my appreciation to the Department of Congenital Heart Surgery team at German Heart Center Munich. The efforts of all involved to show me clinical aspects of my study provided me with practical insights and benefited this dissertation greatly.

Finally, I would like to thank my parents for their support and counsel throughout my time in Munich, without whom this dissertation would not have been possible.

References

Agarwal, A., M. Firdouse, N. Brar, A. Yang, P. Lambiris, A. K. Chan and T. K. Mondal (2018). "Incidence and Management of Thrombotic and Thromboembolic Complications Following the Superior Cavopulmonary Anastomosis Procedure: A Literature Review." Clin Appl Thromb Hemost **24**(3): 405-415.

Agasthi, P. and J. N. Graziano (2021). Pulmonary Artery Banding. StatPearls. Treasure Island (FL).

Alejos, J. C., R. G. Williams, J. M. Jarmakani, A. J. Galindo, J. B. Isabel-Jones, D. Drinkwater, H. Laks and S. Kaplan (1995). "Factors influencing survival in patients undergoing the bidirectional Glenn anastomosis." Am J Cardiol **75**(15): 1048-1050.

Aliyu, I., S. Gambo and P. D. Igoche (2015). "Mitral Atresia with Hypoplastic Left Ventricle and Multiple Shunt Lesions." J Cardiovasc Echogr **25**(3): 77-79.

Allen, P., B. R. Anderson, E. Bacha and D. J. LaPar (2021). "Trisomy 21 Patients Undergoing Cavopulmonary Connections Need Improved Preoperative and Postoperative Care." Ann Thorac Surg **112**(6): 2012-2019.

Alsaied, T., S. Alsidawi, C. C. Allen, J. Faircloth, J. S. Palumbo and G. R. Veldtman (2015). "Strategies for thromboprophylaxis in Fontan circulation: a meta-analysis." Heart **101**(21): 1731-1737.

Alsoufi, B., C. Manlhiot, A. Awan, F. Alfadley, M. Al-Ahmadi, A. Al-Wadei, B. W. McCrindle and Z. Al-Halees (2012). "Current outcomes of the Glenn bidirectional cavopulmonary connection for single ventricle palliation." Eur J Cardiothorac Surg **42**(1): 42-48; discussion 48-49.

Alsoufi, B., M. Mori, S. Gillespie, B. Schlosser, T. Slesnick, B. Kogon, D. Kim, R. Sachdeva and K. Kanter (2015). "Impact of Patient Characteristics and Anatomy on Results of Norwood Operation for Hypoplastic Left Heart Syndrome." Ann Thorac Surg **100**(2): 591-598.

Alsoufi, B., R. Sinha, C. McCracken, J. Figueroa, F. Altin and K. Kanter (2018). "Outcomes and risk factors associated with tricuspid valve repair in children with hypoplastic left heart syndrome." Eur J Cardiothorac Surg **54**(6): 993-1000.

Anderson, P. A., L. A. Sleeper, L. Mahony, S. D. Colan, A. M. Atz, R. E. Breitbart, W. M. Gersony, D. Gallagher, T. Geva, R. Margossian, B. W. McCrindle, S. Paridon, M. Schwartz, M. Stylianou, R. V. Williams, B. J. Clark, 3rd and I. Pediatric Heart Network (2008). "Contemporary outcomes after the Fontan procedure: a Pediatric Heart Network multicenter study." J Am Coll Cardiol **52**(2): 85-98.

Anderson, R. H., A. E. Becker and J. L. Wilkinson (1975). "Proceedings: Morphogenesis and nomenclature of univentricular hearts." Br Heart J **37**(7): 781-782.

Azzolina, G., S. Eufrate and P. Pensa (1972). "Tricuspid atresia: experience in surgical management with a modified cavopulmonary anastomosis." Thorax **27**(1): 111-115.

Barron, D. J., I. U. Haq, A. Crucean, J. Stickley, P. Botha, N. Khan, T. J. Jones and W. J. Brawn (2017). "The importance of age and weight on cavopulmonary shunt (stage II) outcomes after the Norwood procedure: Planned versus unplanned surgery." J Thorac Cardiovasc Surg **154**(1): 228-238.

Biglino, G., A. Giardini, T. Y. Hsia, R. Figliola, A. M. Taylor, S. Schievano and M. C. Group (2013). "Modeling single ventricle physiology: review of engineering tools to study first stage palliation of hypoplastic left heart syndrome." Front Pediatr **1**: 31.

Binotto, M. A., N. Y. Maeda and A. A. Lopes (2005). "Evidence of endothelial dysfunction in patients with functionally univentricular physiology before completion of the Fontan operation." Cardiol Young **15**(1): 26-30.

Bjork, V. O., C. L. Olin, B. B. Bjarke and C. A. Thoren (1979). "Right atrial-right ventricular anastomosis for correction of tricuspid atresia." J Thorac Cardiovasc Surg **77**(3): 452-458.

Blalock, A. and H. B. Taussig (1984). "Landmark article May 19, 1945: The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. By Alfred Blalock and Helen B. Taussig." JAMA **251**(16): 2123-2138.

Blatchford, J. W., 3rd (1985). "Ludwig Rehn: the first successful cardiorrhaphy." Ann Thorac Surg **39**(5): 492-495.

Bleiweis, M. S., J. C. Fudge, G. J. Peek, H. V. Vyas, S. Cruz Beltran, A. D. Pitkin, K. J. Sullivan, J. F. Hernandez-Rivera, J. Philip and J. P. Jacobs (2022). "Ventricular assist device support in neonates and infants with a failing functionally univentricular circulation." JTCVS Tech **13**: 194-204.

Bridges, N. D., R. A. Jonas, J. E. Mayer, M. F. Flanagan, J. F. Keane and A. R. Castaneda (1990). "Bidirectional cavopulmonary anastomosis as interim palliation for high-risk Fontan candidates. Early results." Circulation **82**(5 Suppl): IV170-176.

Carlo, W. F., K. E. Carberry, J. S. Heinle, D. L. Morales, E. D. McKenzie, C. D. Fraser, Jr. and D. P. Nelson (2011). "Interstage attrition between bidirectional Glenn and Fontan palliation in children with hypoplastic left heart syndrome." J Thorac Cardiovasc Surg **142**(3): 511-516.

Cleuziou, J., C. Schreiber, J. K. Cornelsen, J. Horer, A. Eicken and R. Lange (2008). "Bidirectional cavopulmonary connection without additional pulmonary blood flow in patients below the age of 6 months." Eur J Cardiothorac Surg **34**(3): 556-561; discussion 561-552.

Cook, A. C. and R. H. Anderson (2006). "The anatomy of hearts with double inlet ventricle." Cardiol Young **16 Suppl 1**: 22-26.

Craig, B. (2006). "Atrioventricular septal defect: from fetus to adult." Heart **92**(12): 1879-1885.

d'Udekem, Y., A. J. Iyengar, A. D. Cochrane, L. E. Grigg, J. M. Ramsay, G. R. Wheaton, D. J. Penny and C. P. Brizard (2007). "The Fontan procedure: contemporary techniques have improved long-term outcomes." Circulation **116**(11 Suppl): I157-164.

d'Udekem, Y., M. Y. Xu, J. C. Galati, S. Lu, A. J. Iyengar, I. E. Konstantinov, G. R. Wheaton, J. M. Ramsay, L. E. Grigg, J. Millar, M. M. Cheung and C. P. Brizard (2012).

"Predictors of survival after single-ventricle palliation: the impact of right ventricular dominance." J Am Coll Cardiol **59**(13): 1178-1185.

Davies, R. R. and C. Pizarro (2015). "Decision-Making for Surgery in the Management of Patients with Univentricular Heart." Front Pediatr **3**: 61.

de Leval, M. R., P. Kilner, M. Gewillig and C. Bull (1988). "Total cavopulmonary connection: a logical alternative to atriopulmonary connection for complex Fontan operations. Experimental studies and early clinical experience." J Thorac Cardiovasc Surg **96**(5): 682-695.

Dick, M., D. C. Fyler and A. S. Nadas (1975). "Tricuspid atresia: clinical course in 101 patients." Am J Cardiol **36**(3): 327-337.

Feinstein, J. A., D. W. Benson, A. M. Dubin, M. S. Cohen, D. M. Maxey, W. T. Mahle, E. Pahl, J. Villafane, A. B. Bhatt, L. F. Peng, B. A. Johnson, A. L. Marsden, C. J. Daniels, N. A. Rudd, C. A. Caldarone, K. A. Mussatto, D. L. Morales, D. D. Ivy, J. W. Gaynor, J. S. Tweddell, B. J. Deal, A. K. Furck, G. L. Rosenthal, R. G. Ohye, N. S. Ghanayem, J. P. Cheatham, W. Tworetzky and G. R. Martin (2012). "Hypoplastic left heart syndrome: current considerations and expectations." J Am Coll Cardiol **59**(1 Suppl): S1-42.

Fontan, F. and E. Baudet (1971). "Surgical repair of tricuspid atresia." Thorax **26**(3): 240-248.

Forbes, T. J., G. L. Rosenthal, G. R. Reul, Jr., D. A. Ott and T. F. Feltes (1997). "Risk factors for life-threatening cavopulmonary thrombosis in patients undergoing bidirectional superior cavopulmonary shunt: an exploratory study." Am Heart J **134**(5 Pt 1): 865-871.

Frescura, C. and G. Thiene (2014). "The new concept of univentricular heart." Front Pediatr **2**: 62.

Friedman, K. G., J. W. Salvin, D. Wypij, Y. Gurmu, E. A. Bacha, D. W. Brown, P. C. Laussen and M. A. Scheurer (2011). "Risk factors for failed staged palliation after bidirectional Glenn in infants who have undergone stage one palliation." Eur J Cardiothorac Surg **40**(4): 1000-1006.

Frontera Izquierdo, P. and G. Cabezuelo Huerta (1990). "[Natural and unnatural history of the univentricular heart]." Rev Esp Cardiol **43**(6): 381-384.

Ghanayem, N. S., K. R. Allen, S. Tabbutt, A. M. Atz, M. L. Clabby, D. S. Cooper, P. Eghtesady, P. C. Frommelt, P. J. Gruber, K. D. Hill, J. R. Kaltman, P. C. Laussen, A. B. Lewis, K. J. Lurito, L. L. Minich, R. G. Ohye, J. V. Schonbeck, S. M. Schwartz, R. K. Singh, C. S. Goldberg and I. Pediatric Heart Network (2012). "Interstage mortality after the Norwood procedure: Results of the multicenter Single Ventricle Reconstruction trial." J Thorac Cardiovasc Surg **144**(4): 896-906.

Glenn, W. W. and J. F. Patino (1954). "Circulatory by-pass of the right heart. I. Preliminary observations on the direct delivery of vena caval blood into the pulmonary arterial circulation; azygos vein-pulmonary artery shunt." Yale J Biol Med **27**(3): 147-151.

Gobergs, R., E. Salputra and I. Lubaua (2016). "Hypoplastic left heart syndrome: a review." Acta Med Litu **23**(2): 86-98.

Gruenwald, C. E., C. Manlhiot, A. K. Chan, L. Crawford-Lean, C. Foreman, H. M. Holtby, G. S. Van Arsdell, R. Richards, H. Moriarty and B. W. McCrindle (2010). "Randomized, controlled trial of individualized heparin and protamine management in infants undergoing cardiac surgery with cardiopulmonary bypass." J Am Coll Cardiol **56**(22): 1794-1802.

Gruenwald, C. E., C. Manlhiot, L. Crawford-Lean, C. Foreman, L. R. Brandao, B. W. McCrindle, H. Holtby, R. Richards, H. Moriarty, G. Van Arsdell and A. K. Chan (2010). "Management and monitoring of anticoagulation for children undergoing cardiopulmonary bypass in cardiac surgery." J Extra Corpor Technol **42**(1): 9-19.

Gupta-Malhotra, M., V. E. Larson, R. M. Rosengart, H. Guo and J. H. Moller (2010). "Mortality after total cavopulmonary connection in children with the down syndrome." Am J Cardiol **105**(6): 865-868.

Hansen, J. H., A. Uebing, A. K. Furck, J. Scheewe, O. Jung, G. Fischer and H. H. Kramer (2011). "Risk factors for adverse outcome after superior cavopulmonary anastomosis for hypoplastic left heart syndrome." Eur J Cardiothorac Surg **40**(1): e43-49.

Hehir, D. A., T. E. Dominguez, J. A. Ballweg, C. Ravishankar, B. S. Marino, G. L. Bird, S. C. Nicolson, T. L. Spray, J. W. Gaynor and S. Tabbutt (2008). "Risk factors for interstage death after stage 1 reconstruction of hypoplastic left heart syndrome and variants." J Thorac Cardiovasc Surg **136**(1): 94-99, 99 e91-93.

Heidendael, J. F., L. J. Engele, B. J. Bouma, A. I. Dipchand, S. A. Thorne, B. W. McCrindle and B. J. M. Mulder (2022). "Coagulation and Anticoagulation in Fontan Patients." Can J Cardiol **38**(7): 1024-1035.

Hessel, E. A., 2nd (2014). "A Brief History of Cardiopulmonary Bypass." Semin Cardiothorac Vasc Anesth **18**(2): 87-100.

Hopkins, R. A., B. E. Armstrong, G. A. Serwer, R. J. Peterson and H. N. Oldham, Jr. (1985). "Physiological rationale for a bidirectional cavopulmonary shunt. A versatile complement to the Fontan principle." J Thorac Cardiovasc Surg **90**(3): 391-398.

Imai, Y., K. Seo, M. Terada, M. Aoki, T. Shin'oka, J. Ohta and Y. Iwata (1999). "Valvular repair for atrioventricular regurgitation in complex anomalies in modified Fontan procedure with reference to a single ventricle associated with a common atrioventricular valve." Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu **2**: 5-19.

Jacobs, J. P., R. P. Burke, J. A. Quintessenza and C. Mavroudis (2000). "Congenital Heart Surgery Nomenclature and Database Project: atrioventricular canal defect." Ann Thorac Surg **69**(4 Suppl): S36-43.

Jacobs, M. L. and J. E. Mayer, Jr. (2000). "Congenital Heart Surgery Nomenclature and Database Project: single ventricle." Ann Thorac Surg **69**(4 Suppl): S197-204.

Jonas, R. A. (2011). "The intra/extracardiac conduit fenestrated fontan." Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu **14**(1): 11-18.

Kajimoto, H., M. Nakazawa, K. Murasaki, Y. Mori, K. Tanoue, H. Kasanuki and T. Nakanishi (2007). "Increased thrombogenesity in patients with cyanotic congenital heart disease." Circ J **71**(6): 948-953.

Kasnar-Samprec, J., A. Kuhn, J. Horer, M. Vogt, J. Cleuziou, R. Lange and C. Schreiber (2012). "Unloading of right ventricle by bidirectional superior cavopulmonary anastomosis in hypoplastic left heart syndrome patients promotes remodeling of systemic right ventricle but does not improve tricuspid regurgitation." J Thorac Cardiovasc Surg **144**(5): 1102-1108.

Khairy, P., S. M. Fernandes, J. E. Mayer, Jr., J. K. Triedman, E. P. Walsh, J. E. Lock and M. J. Landzberg (2008). "Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery." Circulation **117**(1): 85-92.

Khairy, P., N. Poirier and L. A. Mercier (2007). "Univentricular heart." Circulation **115**(6): 800-812.

Kogon, B. (2012). "Is the extracardiac conduit the preferred Fontan approach for patients with univentricular hearts? The extracardiac conduit is the preferred Fontan approach for patients with univentricular hearts." Circulation **126**(21): 2511-2515; discussion 2515.

Kreutzer, G., E. Galindez, H. Bono, C. De Palma and J. P. Laura (1973). "An operation for the correction of tricuspid atresia." J Thorac Cardiovasc Surg **66**(4): 613-621.

Krishna, R. and M. Rudrappa (2022). Pleural Effusion. StatPearls. Treasure Island (FL).

Kushner, A., W. P. West and L. S. Pillarisetty (2021). Virchow Triad. StatPearls. Treasure Island (FL).

Laks, H., R. N. Gates, A. Elami and J. M. Pearl (1992). "Damus-Stansel-Kaye procedure: technical modifications." Ann Thorac Surg **54**(1): 169-172.

Lange, R. and J. Horer (2010). Funktionell singulärer Ventrikel und Fontan Operation. Herzchirurgie. G. Ziemer and A. Haverich. Berlin Heidelberg New York Springer. **3:** 331–361.

Lee, D., H. C. Moon, B. T. Tran, D. H. Kwon, Y. H. Kim, S. D. Jung, J. H. Joo and Y. S. Park (2018). "Characterization of Tetrodes Coated with Au Nanoparticles (AuNPs) and PEDOT and Their Application to Thalamic Neural Signal Detection in vivo." Exp Neurobiol **27**(6): 593-604.

Lee, T. M., R. Aiyagari, J. C. Hirsch, R. G. Ohye, E. L. Bove and E. J. Devaney (2012). "Risk factor analysis for second-stage palliation of single ventricle anatomy." Ann Thorac Surg **93**(2): 614-618; discussion 619.

Lefemine, A. A. and D. E. Harken (1966). "Postoperative care following open-heart operations: routine use of controlled ventilation." J Thorac Cardiovasc Surg **52**(2): 207-216.

Leschka, S., E. Oechslin, L. Husmann, L. Desbiolles, B. Marincek, M. Genoni, R. Pretre, R. Jenni, S. Wildermuth and H. Alkadhi (2007). "Pre- and postoperative evaluation of congenital heart disease in children and adults with 64-section CT." Radiographics **27**(3): 829-846.

Liu, J., Y. Lu, H. Chen, Z. Shi, Z. Su and W. Ding (2004). "Bidirectional Glenn procedure without cardiopulmonary bypass." Ann Thorac Surg **77**(4): 1349-1352.

Mahle, W. T., M. S. Cohen, T. L. Spray and J. Rychik (2001). "Atrioventricular valve regurgitation in patients with single ventricle: impact of the bidirectional cavopulmonary anastomosis." Ann Thorac Surg **72**(3): 831-835.

Manlhiot, C., L. R. Brandao, J. Kwok, S. Kegel, I. B. Menjak, C. L. Carew, A. K. Chan, S. M. Schwartz, V. B. Sivarajan, C. A. Caldarone, G. S. Van Arsdell and B. W. McCrindle (2012). "Thrombotic complications and thromboprophylaxis across all three stages of single ventricle heart palliation." J Pediatr **161**(3): 513-519 e513.

Marcelletti, C., A. Corno, S. Giannico and B. Marino (1990). "Inferior vena cava-pulmonary artery extracardiac conduit. A new form of right heart bypass." J Thorac Cardiovasc Surg **100**(2): 228-232.

Meza, J. M., E. Hickey, B. McCrindle, E. Blackstone, B. Anderson, D. Overman, J. K. Kirklin, T. Karamlou, C. Caldarone, R. Kim, W. DeCampli, M. Jacobs, K. Guleserian, J. P. Jacobs, R. Jaquiss and S. P. W. G. Congenital Heart Surgeons' Society Timing of (2018). "The Optimal Timing of Stage-2-Palliation After the Norwood Operation." Ann Thorac Surg **105**(1): 193-199.

Minocha, P. K. and C. Phoon (2022). Tricuspid Atresia. StatPearls. Treasure Island (FL).

Mir, A., S. Frank, J. Journeycake, J. Wolovitis, K. Guleserian, L. Heistein and M. Lemler (2015). "Aspirin Resistance in Single-Ventricle Physiology: Aspirin Prophylaxis Is Not Adequate to Inhibit Platelets in the Immediate Postoperative Period." Ann Thorac Surg **99**(6): 2158-2164.

Mitchell, M. B., D. N. Campbell, M. M. Boucek, H. M. Sondheimer, K. C. Chan, D. D. Ivy, B. Pietra and T. Mackenzie (2003). "Mechanical limitation of pulmonary blood flow facilitates heart transplantation in older infants with hypoplastic left heart syndrome." Eur J Cardiothorac Surg **23**(5): 735-742.

Monagle, P., A. K. C. Chan, N. A. Goldenberg, R. N. Ichord, J. M. Journeycake, U. Nowak-Gottl and S. K. Vesely (2012). "Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines." Chest **141**(2 Suppl): e737S-e801S.

Moodie, D. S., D. G. Ritter, A. J. Tajik and W. M. O'Fallon (1984). "Long-term follow-up in the unoperated univentricular heart." Am J Cardiol **53**(8): 1124-1128.

Morlando, M., A. Bhide, A. Familiari, A. Khalil, J. Morales-Rosello, A. T. Papageorghiou and J. S. Carvalho (2017). "The association between prenatal atrioventricular septal defects and chromosomal abnormalities." Eur J Obstet Gynecol Reprod Biol **208**: 31-35.

Morray, B. H., E. L. Albers, T. K. Jones, M. S. Kemna, L. C. Permut and Y. M. Law (2018). "Hybrid stage 1 palliation as a bridge to cardiac transplantation in patients with high-risk single ventricle physiology." Pediatr Transplant **22**(8): e13307.

Muller, W. H., Jr. and J. F. Dammann, Jr. (1952). "The surgical significance of pulmonary hypertension." Ann Surg **136**(3): 495-509.

Nakano, T., H. Kado, H. Tatewaki, K. Hinokiyama, S. Oda, H. Ushinohama, K. Sagawa, M. Nakamura, N. Fusazaki and S. Ishikawa (2015). "Results of extracardiac conduit total cavopulmonary connection in 500 patients." Eur J Cardiothorac Surg **48**(6): 825-832; discussion 832.

O'Leary, P. W. (2002). "Prevalence, clinical presentation and natural history of patients with single ventricle." Progress in Pediatric Cardiology **16**(1): 31-38.

Odegard, K. C., F. X. McGowan, Jr., J. A. DiNardo, R. A. Castro, D. Zurakowski, C. M. Connor, D. D. Hansen, E. J. Neufeld, P. J. del Nido and P. C. Laussen (2002). "Coagulation abnormalities in patients with single-ventricle physiology precede the Fontan procedure." J Thorac Cardiovasc Surg **123**(3): 459-465.

Ono, M., J. Kasnar-Samprec, A. Hager, J. Cleuziou, M. Burri, C. Langenbach, A. Callegari, M. Strbad, M. Vogt, J. Horer, C. Schreiber and R. Lange (2016). "Clinical outcome following total cavopulmonary connection: a 20-year single-centre experience." Eur J Cardiothorac Surg **50**(4): 632-641.

Ota, N., T. Tachibana, H. Asai, J. Ikarashi, T. Asou and H. Izutani (2020). "Outcomes of bidirectional cavopulmonary shunt in patients younger than 4 months of age." Eur J Cardiothorac Surg **57**(5): 937-944.

Overman, D. M., K. B. Dummer, F. X. Moga and D. B. Gremmels (2013). "Unbalanced atrioventricular septal defect: defining the limits of biventricular repair." Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu **16**(1): 32-36.

Owens, G. E., C. Gomez-Fifer, S. Gelehrter and S. T. Owens (2009). "Outcomes for patients with unbalanced atrioventricular septal defects." Pediatr Cardiol **30**(4): 431-435.

Pabst von Ohain, J., E. Tonino, H. Kaemmerer, J. Cleuziou, P. Ewert, R. Lange and J. Horer (2021). "German Heart Centre Munich-45 years of surgery in adults with congenital heart defects: from primary corrections of septal defects and coarctation to complex reoperations." Cardiovasc Diagn Ther **11**(2): 492-502.

Paget, S. (1896). "The Surgery of the Chest." Hospital (Lond 1886) **19**(485): 121.

Park, M. (2020). Park's Pediatric Cardiology for Practitioners, Elsevier.

Pujol, C., A. C. Niesert, A. Engelhardt, P. Schoen, E. Kusmenkov, D. Pittrow, P. Ewert and H. Kaemmerer (2016). "Usefulness of Direct Oral Anticoagulants in Adult Congenital Heart Disease." Am J Cardiol **117**(3): 450-455.

Raju, V., J. A. Dearani, H. M. Burkhart, M. Grogan, S. D. Phillips, N. Ammash, R. P. Pike, J. N. Johnson and P. W. O'Leary (2014). "Right ventricular unloading for heart failure related to Ebstein malformation." Ann Thorac Surg **98**(1): 167-173; discussion 173-164.

Rao, P. S. (2019). "Management of Congenital Heart Disease: State of the Art-Part II-Cyanotic Heart Defects." Children (Basel) **6**(4).

Ravn, H. B., V. E. Hjortdal, E. V. Stenbog, K. Emmertsen, O. Kromann, J. Pedersen and K. E. Sorensen (2001). "Increased platelet reactivity and significant changes in coagulation markers after cavopulmonary connection." Heart **85**(1): 61-65.

Ricci, M., P. Lombardi, A. Galindo, A. Vasquez, J. Zuccarelli and E. Rosenkranz (2005). "Distribution of cardiac output and oxygen delivery in an acute animal model of single-ventricle physiology." J Thorac Cardiovasc Surg **130**(4): 1062-1070.

Ruiz, C. E., H. Gamra, H. P. Zhang, E. J. Garcia and M. M. Boucek (1993). "Brief report: stenting of the ductus arteriosus as a bridge to cardiac transplantation in infants with the hypoplastic left-heart syndrome." N Engl J Med **328**(22): 1605-1608.

Samanek, M. (1992). "Children with congenital heart disease: probability of natural survival." Pediatr Cardiol **13**(3): 152-158.

Sarkar, M. and V. Prabhu (2017). "Basics of cardiopulmonary bypass." Indian J Anaesth **61**(9): 760-767.

Scheurer, M. A., E. G. Hill, N. Vasuki, S. Maurer, E. M. Graham, V. Bandisode, G. S. Shirali, A. M. Atz and S. M. Bradley (2007). "Survival after bidirectional cavopulmonary anastomosis: analysis of preoperative risk factors." J Thorac Cardiovasc Surg **134**(1): 82-89, 89 e81-82.

Schilling, C., K. Dalziel, R. Nunn, K. Du Plessis, W. Y. Shi, D. Celermajer, D. Winlaw, R. G. Weintraub, L. E. Grigg, D. J. Radford, A. Bullock, T. L. Gentles, G. R. Wheaton, T. Hornung, R. N. Justo and Y. d'Udekem (2016). "The Fontan epidemic: Population projections from the Australia and New Zealand Fontan Registry." Int J Cardiol **219**: 14-19.

Schreiber, C., J. Cleuziou, J. K. Cornelsen, J. Horer, A. Eicken and R. Lange (2008). "Bidirectional cavopulmonary connection without additional pulmonary blood flow as an ideal staging for functional univentricular hearts." Eur J Cardiothorac Surg **34**(3): 550-554 ;discussion 554-555.

Schreiber, C., M. Kostolny, J. Weipert, K. Holper, M. Vogt, A. Hager, F. Haas, J. Hess and R. Lange (2004). "What was the impact of the introduction of extracardiac completion for a single center performing total cavopulmonary connections?" Cardiol Young **14**(2): 140-147.

Schwartz, M. C., M. A. Brock, D. Nykanen and W. DeCampli (2018). "Risk Factors for an Elevated Ventricular End-Diastolic Pressure Prior to the Fontan Operation." Pediatr Cardiol **39**(2): 315-323.

Schwedler, G., A. Lindinger, P. E. Lange, U. Sax, J. Olchvary, B. Peters, U. Bauer and H. W. Hense (2011). "Frequency and spectrum of congenital heart defects among live births in Germany : a study of the Competence Network for Congenital Heart Defects." Clin Res Cardiol **100**(12): 1111-1117.

Sharma, R. (2000). "Surgical therapy for the univentricular heart." Indian J Pediatr **67**(3 Suppl): S37-40.

Spray, T. L. (2013). "Hemi-Fontan Procedure." Operative Techniques in Thoracic and Cardiovascular Surgery **18**(2): 124-137.

Stumper, O. and G. Penford (2017). "Catheter hemodynamic assessment of the univentricular circulation." Ann Pediatr Cardiol **10**(2): 167-174.

Talwar, S., V. V. Nair, S. K. Choudhary and B. Airan (2014). "The Hemi-Fontan operation: A critical overview." Ann Pediatr Cardiol **7**(2): 120-125.

Tandon, R. and J. E. Edwards (1974). "Tricuspid atresia. A re-evaluation and classification." J Thorac Cardiovasc Surg **67**(4): 530-542.

Tchervenkov, C. I., M. L. Jacobs and S. A. Tahta (2000). "Congenital Heart Surgery Nomenclature and Database Project: hypoplastic left heart syndrome." Ann Thorac Surg **69**(4 Suppl): S170-179.

Todd Tzanetos, D. R., C. Yu, M. Hernanz-Schulman, F. E. Barr and N. J. Brown (2012). "Prospective study of the incidence and predictors of thrombus in children undergoing palliative surgery for single ventricle physiology." Intensive Care Med **38**(1): 105-112.

Tomkiewicz-Pajak, L., T. Wojcik, S. Chlopicki, M. Olszowska, J. Pajak, J. Podolec, B. Sitek, P. Musialek, P. Rubis, M. Komar and P. Podolec (2015). "Aspirin resistance in adult patients after Fontan surgery." Int J Cardiol **181**: 19-26.

Tran, S., P. M. Sullivan, J. Cleveland, S. R. Kumar and C. Takao (2018). "Elevated Pulmonary Artery Pressure, Not Pulmonary Vascular Resistance, is an Independent Predictor of Short-Term Morbidity Following Bidirectional Cavopulmonary Connection." Pediatr Cardiol **39**(8): 1572-1580.

Van Den Helm, S., C. N. Sparks, V. Ignjatovic, P. Monagle and C. Attard (2022). "Increased Risk for Thromboembolism After Fontan Surgery: Considerations for Thromboprophylaxis." Front Pediatr **10**: 803408.

Vanpraagh, R., P. A. Ongley and H. J. Swan (1964). "Anatomic Types of Single or Common Ventricle in Man. Morphologic and Geometric Aspects of 60 Necropsied Cases." Am J Cardiol **13**: 367-386.

Vricella, L. A., P. Samankatiwat, M. R. de Leval, V. T. Tsang and P. R. Vouhe (2004). "Simplified antegrade cerebral perfusion and myocardial protection during stage I Norwood procedure." Asian Cardiovasc Thorac Ann **12**(4): 372-373.

Weerasinghe, A. and K. M. Taylor (1998). "The platelet in cardiopulmonary bypass." Ann Thorac Surg **66**(6): 2145-2152.

Weichert, J., R. Axt-Fliedner, U. Gembruch and D. R. Hartge (2013). "Holmes heart--a simple antenatal diagnosis of a complex cardiac anomaly? Fetal echocardiographic findings and review." Congenit Heart Dis **8**(6): 579-584.

West, C., T. Maul, B. Feingold and V. O. Morell (2019). "Right Ventricular Dominance Is Associated With Inferior Outcomes After the Extracardiac Fontan." World J Pediatr Congenit Heart Surg **10**(4): 416-423.

Yabrodi, M. and C. W. Mastropietro (2017). "Hypoplastic left heart syndrome: from comfort care to long-term survival." Pediatr Res **81**(1-2): 142-149.

Yamagishi, S., A. Masuoka, Y. Uno, T. Katogi and T. Suzuki (2014). "Influence of bidirectional cavopulmonary anastomosis and concomitant valve repair on atrioventricular valve annulus and function." Ann Thorac Surg **98**(2): 641-647; discussion 647.