Aus der Klinik für Herz-, Thorax- und Gefäßchirurgie
des Deutschen Herzzentrums Berlin
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Clinical Analysis and Preoperative Predictors of Survival in Children after Ventricular Assist Device Implantation

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

Von

Ye Fan

aus Chongqing, V.R. China

Gutachter/in: 1. Prof. Dr. med. Johannes Albes

2. Prof. Dr. med. Hermann Eichstädt

3. Dr. med. Rufus Baretti

Datum der Promotion: 09.09.2011

Contents

Abbreviations and Acronyms

CHD	congenital heart disease
CHF	congestive heart failure
ECMO	extracorporeal membrane oxygenation
IABP	intra-aortic balloon pump
VAD	ventricular assist device
BSA	body surface area
ELSO	Extracorporeal Life Support Organization
RVAD	right ventricular assist device
LVAD	left ventricular assist device
BiVAD	biventricular assist device
PTT	partial thromboplastin time
DHZB	Deutsches Herzzenturm Berlin
BNP	B-type natriuretic peptide
INR	international normalized ratio
ICU	intensive care unit
CPR	cardiopulmonary resuscitation
SpO_2	pulse oxygen saturation
CVP	central venous pressure
PCWP	pulmonary capillary wedge pressure
LVEF	left ventricular ejection fraction
ALT	alanine aminotransferase activity
AST	aspartate aminotransferase activity
LDH	lactate dehydrogenase
CK-MB	creatine kinase-MB
GGT	γ-glutamyl transpeptadase
BUN	blood urea nitrogen
CRP	C-reactive protein
UniVAD	univentricular assist device
OR	odds ratios
CI	confidence interval
CPB	cardiopulmonary bypass

1. Introduction

1.1 Mechanical circulatory support in the pediatric population

1.1.1 General history

According to the Dimes study carried out in 193 countries in 2006, approximately eight million children are born each year with serious heart defects needing surgical interventions (1). It has been reported that about one million children are born each year with congenital heart disease (CHD) which requires corrective treatment in USA alone. Of those, approximately 40,000 children need surgical intervention within the first few days to years of life (2). Based on the registry of the International Society of Heart and Lung Transplantation, around 65% of cardiac transplantations in infants are performed because of severe cardiac defects, and the proportion reduces to 24% in older patients (3, 4). The end-stage of CHD is congestive heart failure (CHF), and current medical treatment is marginally successful, resulting in increasing requirements for heart transplantation. However, the extreme shortage of suitable donors in children complicates cardiac transplantation and prolongs the waiting time, leading to increased death rates in those patients (5, 6). Clinicians who care for children must contend with these complications, since mortality is more than 5% in those neonates who were on waiting list but unable to receive transplantation by 6 months of age.

A lot of pediatric patients with complex CHD are also developing cardiomyopathies. It has been estimated that about 1 per 100,000 children each year was affected by cardiomyopathy (7, 8), which could be caused by inherited muscular diseases, metabolic and mitochondrial defects, viral myocarditis, or cardiac arrhythmias (7). Cardiomyopathy leads to impaired ventricular function, and is the most common cause of myocardial failure in pediatric patients (9, 10). Current therapies include conventional catecholamines and several new pharmacologic agents (such as milrinone), which may lead to symptomatic improvement of patients, but could not halt progression of the disease.

The usage of mechanical circulatory support in pediatric patients with congenital or acquired cardiac disease has been continuously increasing over the past decade (11). Extracorporeal membrane oxygenation (ECMO) is currently the most common method of mechanical

circulatory assistance in children (12-14). Intra-aortic balloon pumps (IABPs) could also be used to provide temporary support for some older and larger children (12-15). However, the major disadvantage of these support options is that they could not provide long-term mechanical circulatory support in pediatric patients (12-15).

Ventricular assist device (VAD) is a well-established therapy for adult patients with end-stage heart disease. Using VAD support as a bridge to transplantation or myocardial recovery has yielded encouraging long-term outcomes. These blood pumps could typically supplement the output of the native ventricle, and meanwhile unload the systemic ventricle. For pediatric patients, VAD is also a valid option for providing long-term mechanical circulatory assistance, and its clinical use in children has been steadily increasing (3, 11-17). However, most of the currently available VADs were designed for adult support. Although they lead to perfect clinical results in adult recipients, they are not suitable for providing mechanical circulatory support in small infants and young children with end-stage heart disease.

The earliest report of VAD use in a pediatric patient dates back to 1967. DeBakey and his colleagues inserted a left atrial-axillary artery ventricular assist device into a teenage child with postcardiotomy failure. The child recovered after 6 months (12). During the 1970s, centrifugal pumps, such as the BioMedicus Biopump (Medtronic, Minneapolis, MN), were the most commonly used mechanical circulatory assist devices in pediatric patients, which results in profound clinical outcomes (18). However, the centrifugal pump VAD had a number of inherent limitations similar to ECMO. It provided non-pulsatile blood flow, and was only suitable for a short time of support.

During the early 1990s, with the increased VAD experience in adult patients with end-stage heart disease, several adult paracorporeal ventricular assist devices, such as the Thoratec VADs (Thoratec Laboratories Corp) and Abiomed BVS 5000 (Abiomed Inc., Danvers, MA), started to be implanted into intermediate-size children despite the size discrepancy (19, 20). Many studies have reported their results and experiences of using pulsatile paracorporeal device which were designed for adult applications in older pediatric patients. According to a retrospective, multi-institutional study, Blume et al. have found that 86% of children with VAD support could be successfully bridged to transplantation (11).

However, although the clinical results of applying adult-sized ventricular assist devices in children were generally good, they were associated with an increased incidences of thromboembolic and hemorrhagic neurologic events, particularly in smaller children with body surface area (BSA) < 1.3 m^2 (19). These findings supported the conclusion that patient size plays an important role in device selection, and postimplantation anticoagulation therapy is a particular challenge in small children.

During the past decade, the Berlin Heart EXCOR pediatric ventricular assist devices which were designed for pediatric patients of all ages have entered the clinical realm. Although the earliest reports of the application of the Berlin Heart EXCOR pediatric VAD were also associated with high thromboembolic risk, subsequent improvements in pump and cannual design and better anticoagulation therapy have significantly decreased the incidences of these morbidities.

1.1.2 Extracorporeal membrane oxygenation

Mechanical support with extracorporeal membrane oxygenation in children has been performed successfully since 1975 (21). Until now, ECMO is still the most commonly used form of pediatric mechanical circulatory support in the world; more than 3500 cases of pediatric cardiac ECMO have been recorded in the registry of the Extracorporeal Life Support Organization (ELSO) (22-24). The ability to provide support for even the smallest patients and the experience in pediatric hospitals in the management of newborn respiratory failure are the two main reasons for the widespread use of ECMO in the treatment of children with end-stage heart failure. In fact, ECMO is at present the only available form of mechanical circulatory support for children at many centers in the world. With the presence of an oxygenator, ECMO remains the best support option for cases complicated by hypoxemia and respiratory failure, and its ability to be instituted through peripheral cannulation makes it particularly useful for acute resuscitation (25). It is frequently the first choice of support for patients with intracardiac defects, concomitant respiratory failure, and unknown potential for recovery from shock-induced organ dysfunction, because the technique represents a flexible emergency rescue system. Additional left atrial venting or balloon atrial septostomy allows complete cardiac decompression.

Nevertheless, ECMO also has a number of inherent limitations: its use is restricted to short-term applications, and its extracorporeal design precludes ambulation and effective physical rehabilitation during support. In addition, the presence of an oxygenator and long tubing lengths

in the circuit excessively damage blood elements and activate the inflammatory cascade. All of these factors contribute to the high mortality rate of nearly 60% that has been consistently observed in pediatric cardiac patients who require ECMO support (21). The ELSO registry data showed an overall survival to discharge of 65% in the current era, but the numbers for cardiac patients are at best, 50%. The best outcomes occurred after short-term use for less than 1 week. Currently, actively discussed issues in pediatric cardiac ECMO include pulsatile flow ECMO (26), early initiation and the concept of 'bridge to bridge' therapy (27, 28-31).

1.1.3 Centrifugal ventricular assist devices

The currently available centrifugal pump VADs are BioMedicus Biopump, (Medtronic, Minneapolis, MN), Levitronix CentriMag (Levitronix, Zürich, Switzerland), RotaFlow (Jostra, Hirrlingen, Germany), and Capiox (Terumo, Ann Arbor, MI). Since 1989, centrifugal VAD has been used to support pediatric patients with postoperative cardiac failure but non-impaired lung function. Based on vortex technology, these VAD systems use turbine spins of 10,000-20,000 rpm to create a flow of 5-6 l/min and have generally been applied for temporary assistance of stunned myocardium of the left ventricle (18, 32-35). The centrifugal VAD system can be used to support pediatric patients of all ages and can be used as a right ventricular assist device (RVAD), left ventricular assist device (LVAD), or biventricular assist device (BiVAD).

Centrifugal VADs have several advantages over other mechanical circulatory assist devices: they did not need oxygenator, and have low priming volume and low requirements for heparin and hemolysis. They could efficiently decompress the ventricles, and patient transport is convenient and the costs are relatively low. However, the centrifugal system is not suitable for patients with severely impaired lung function. Furthermore, most of the pediatric patients receiving centrifugal VAD support must leave their chest open after operation, and thus should be constantly sedated and mechanically ventilate. Duncan et al. have recently reported their results of 29 children supported with BioMedicus VADs (24). The survival rate was 71% in children with anomalous origin of the left coronary artery from the pulmonary artery or with cardiomyopathy, and the posttransplantation survival was 50%. Other common postimplantation morbidities are recurrent bleeding, thrombosis and infections, which usually take place in 2-3 weeks after centrifugal VAD insertion. Thuys et al. reported their experience of applying centrifugal pump in 34 pediatric patients with congenital heart diseases and weighed less than 6 kg (18). In their study,

64% of the children could wean from the VAD support, and the overall survival to discharge was 31%.

1.1.4 Long-term ventricular assist devices

Ventricular assist devices can provide longer term support for patients with end-stage heart disease. There are two major categories: paracorporeal and intracorporeal devices. Paracorporeal devices include: the Berlin Heart EXCOR VAD (Berlin Heart AG, Berlin, Germany), Thoratec ventricular assist device (Thoratec Laboratories Corp), Abiomed BVS 5000 and Abiomed AB 5000 (Abiomed Inc., Danvers, MA), and MEDOS HIA VAD (MEDOS Medizintechnik AG, Stolberg, Germany). Intracorporeal devices include: the Berlin Heart Incor. (Berlin Heart AG, Berlin, Germany), the MicroMed DeBakey VAD (MicroMed Technology, Inc, Houston, Tex), the Jarvik 2000 Flowmaker (Jarvik Heart Inc, New York, NY), the Thoratec Heartmate II VAD (Thoratec Laboratories Corp), the HeartWare HVAD (HeartWare Inc, Framingham, MA), and the Evaheart (SunMedical Technology Research, Nagano, Japan).

Pulsatile excoporeal VADs

Only the Berlin Heart Excor and the Medos HIA pulsatile systems could provide successful long-term support in children of all ages (however, the Medos VAD is allowed to only provide up to 30 days supports) (36-42). The two systems are both extracorporeal and consist of a pneumatic compressor-operated diaphragm pump with valves. The two devices have transparent polyurethane pump housings, which allow clinicians to detect thrombus in early period. The external position of the ventricles allows fast and safe exchanges of the pump. Currently, the results for the Medos HIA have only been reported in a small series of children (37, 40-41); for the Berlin Heart Excor, more results are available (43-45).

Several other pulsatile devices which were developed for adult patients can also be applied in school-age children and adolescents, including the HeartMate I (Thoratec Laboratories Corp), Toyobo (Toyobo-National Cardiovascular Center, Osaka, Japan), and Novacor (WorldHeart Corp., Oakland, CA). Use of these devices in adolescents and older children has resulted in encouraging clinical outcomes (12, 46-49). However, the major disadvantage of these devices is that they can not provide support for patients with body surface area less than 1.2 m^2, and require pump flows of more than 2 l/min.

Continuous-flow ventricular assist devices

Several continuous-flow rotary VADs which generate centrifugal or axial flow, such as the INCOR VAD, the DeBakey VAD, the HeartMate II VAD, and the HeartWare HVAD, have been routinely used in adult patients with end-stage heart failure (52-53). In selected cases, they could be applied in some older and larger children.

1.2 Berlin Heart EXCOR pediatric ventricular assist device

1.2.1 Structure

The Berlin Heart EXCOR ventricular assist device was developed by Hetzer et al. in collaboration with the Berlin Heart Company, and was worldwide the first pulsatile paracorporeal VAD to successfully bridge a pediatric patient to cardiac transplantation. It consists of a paracorporeal, pneumatic compressor-operated diaphragm pump with valves, silicone cannulas, and the IKUS stationary driving unit. The Excor mobile driving unit (Berlin Heart AG) can be utilized in larger pumps with driving pressures lower than 250 mmHg.

Blood pumps

The blood pumps are available in sizes of 10, 25, 30, 50, 60, and 80 mL (Fig 5A). The pumps with 10 mL volume provide effective mechanical circulatory support in neonates and small infants with weight of up to 9 kg (body surface area 0.43 m^2). The pumps with volumes of 25 and 30 mL are suitable for children aged up to 7 years (weight 30 kg and body surface area of around 0.95 m^2). The adult sized pumps (50, 60, and 80 mL) could be applied in older children with larger weight and body surface area (Figure 1). The blood pump consists of a translucent, semirigid housing made of polyurethane (54), with a multilayer flexible polyurethane membrane separating this pump chamber into a blood and an air chamber. The two diaphragm layers facing the air chamber serve as driving membranes. The seamless cast-on blood membrane is passively moved by the driving membranes.

The cannula is connected to a deairing nipple integrated into the blood chamber, in order to eliminate residual air after pump insertion. The trifleaflet valves made of polyurethane are mounted in the pediatric sized pumps (10, 25, 30 mL), preventing blood reflux. For the adult sized pumps (50, 60, 80 mL), both tilting disc valves (Sorin Biomedical, Torino, Italy) and trileaflet polyurethane valves are available. Figure 1B shows the cross-section of the pump. All blood-contacting surfaces inside the pump, including the polyurethane valves, are coated with heparin (Carmeda; Texas, USA), in order to provide efficient protection against thrombosis. Since 1994, this technique has been routinely used in our center, and has proved to be effective for as long as 6 months after VAD insertion (55-57).

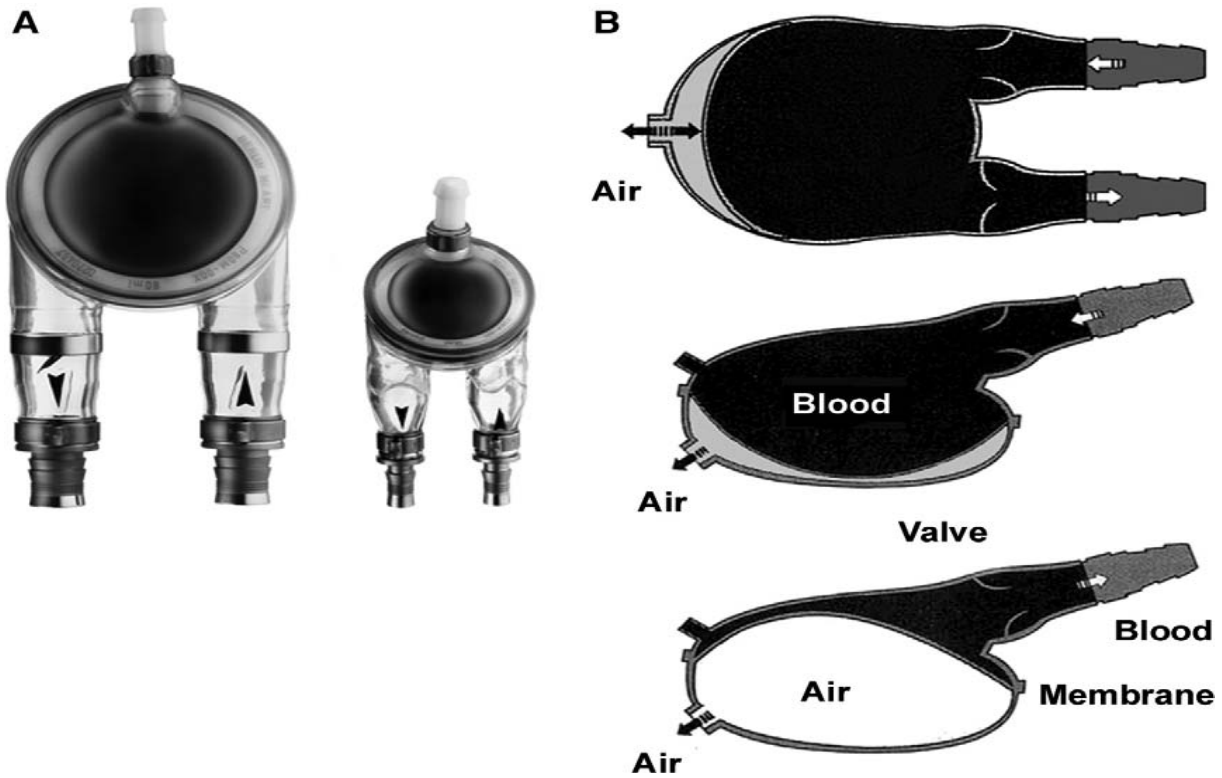

Figure 1 (A) Berlin Heart pumps with 10 mL and 80 mL stroke volume. (B) Cross-section of the Berlin Heart EXCOR pump.

Cannulas

The Berlin Heart Excor cannulas are made of silicone rubber with an extremely smooth internal surface. For supporting the right heart, blood is drained from the right atrium and ejected into the pulmonary artery. On the left side, cannulas are introduced into either the left atrium or the left ventricular apex (Figure 2), and connected to the ascending aorta. For some adult recipients, cannulas for left ventricular apex drainage and connection to the descending aorta are also available.

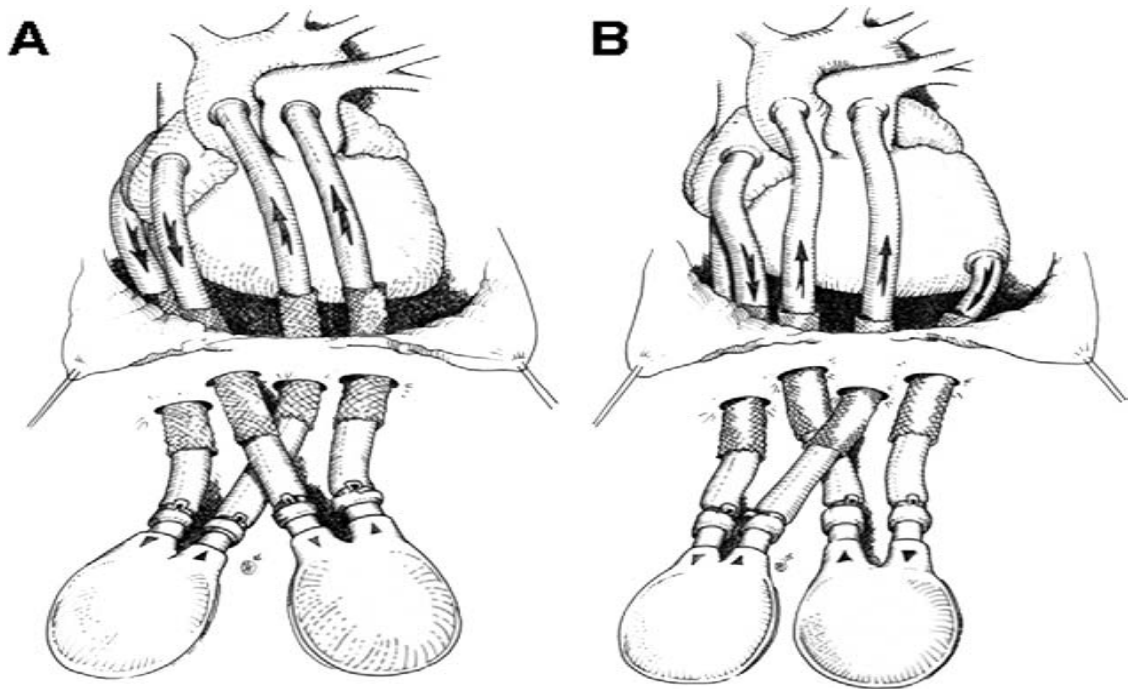

Figure 2. Modes of implantation of the Berlin Heart Excor biventricular assist device. (A) In the earlier period, atrial cannulation was the rule. (B) More recently, apical cannulation was introduced and is now preferred owing to better left ventricular unloading and reduced afterload to the right ventricle. Consequently, in many instances, a left ventricular assist device only is sufficient.

The cannulas of the Berlin Heart EXCOR VAD have a variety of designs and diameters, in order to match different patient sizes and anatomies (Figure 3). Cannulas with internal diameters of 4.8, 6, and 9 mm are available for children. For adult recipients, cannulas with internal diameters of 12 mm are available. A Dacron velour (C. R. Bard, Haverhill, Pennsylvania) covers the outside of the cannulas at the contact site with the abdominal wall, stimulating scar tissue ingrowth and thereby preventing ascending infections. The larger atrial cannulas with different-sized cages for insertion into the atrium are available for adult patients. Their lengths range from 22 to 26 mm, in order to match the variations in wall thickness. The smaller pediatric size cannulas are manufactured with standard cage lengths. Various apical cannulas for left ventricle cannulation are available for all patient sizes and age groups, which significantly improves drainage of the left ventricle.

All sewing rings of the cannulas are covered by a Dacron felt. The suture technique includes 8 to 10 Teflon (Impra, subsidiary of L. R. Bard, Tempe, AZ) felt enforced sutures and an additional purse string suture. On the arterial cannulas for neonates and small infants, there is a short titanium re-enforced tip for insertion into the blood vessel wall, the so-called “press-button” tip. These cannulas could significantly reduce the afterload to the native heart, as compared to the

conventional cannulas of the heart-lung machine. All cannulas of the Berlin Heart Excor ventricular assist device exit the patients' body via the upper abdominal wall.

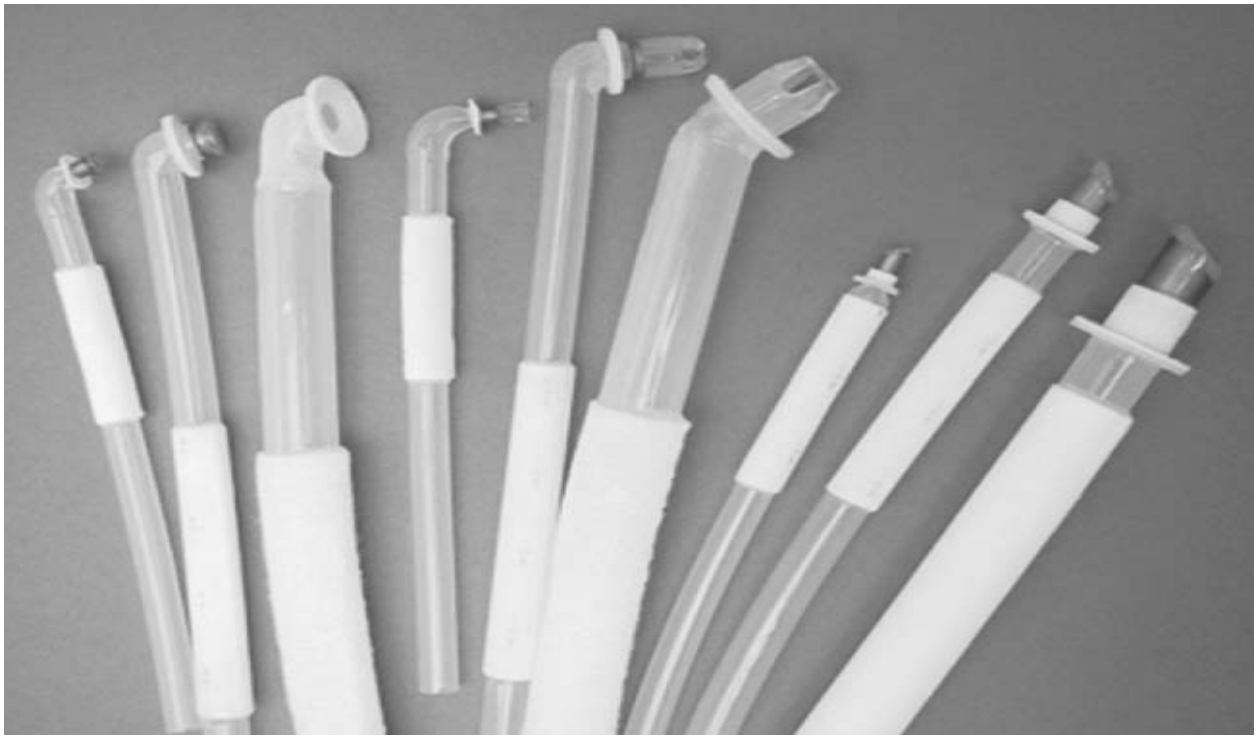

Figure 3. The set of cannulas available for the Berlin Heart support system. The cannulas differ in diameter, length, and configuration of the tip. The availability of different tips allows blood drainage from the left atrium or the left ventricular apex.

Driving unit

The Berlin Heart Excor pediatric VAD is powered by the IKUS driving unit. The pump diaphragm is moved into its endsystolic position by compressed air, thus ejecting the blood stroke volume. Negative pressure is generated by pump diastole, which assists blood refilling of the pump. The driving unit has three compressor units: one for the left pump, one for the right pump, and one back-up compressor which will take over automatically without delay when there is malfunction of the original compressor unit. In case both compressor units suddenly lose their function, the third compressor unit can generate an acceptable pump output for both pumps with a rate of 90 beats per minute. Two redundant internal computers manage the actions of the compressor and pressure / vacuum regulator. User control is available with a personal computer. An internal battery could provide DC power for up to 1 hour. The maximum positive driving pressure is 350mmHg, whereas the maximum negative driving pressure is -100mm Hg. The

excessive pressures are necessarily required, in order to overcome the resistances of the pediatric cannulas. The pump rate can be adjusted according to the personal needs of pediatric patients (range from 30 to 150 beats per minute), and the relative systolic duration could vary from 20% to 70%.

The driving system has two modes: univentricular and biventricular. There are three options for the pump action in biventricular mode: “synchronous” for simultaneous, “asynchronous” for alternating, and “separate” for independent pump action. The driving system allows for independent control of pump rate, systolic pump pressure, diastolic pump pressure, and length of systole of each side, which is extremely critical for recovery of the right ventricle. In this case, the right pump output should be decreased to prevent lung edema.

1.3 Indications for VAD implantation in the pediatric population

1.3.1 Cardiomyopathy

For children in whom all intensive pharmacologic treatment fails, a long-term VAD implantation should be considered, mainly as bridge to heart transplantation. Since the waiting time is unpredictable, if they do not receive mechanical support, mortality for these children could be very high while they are waiting for donor hearts (44). In addition, children have a greater possibility of complete myocardial recovery with VAD support than adult patients, allowing pump explantation and the prospect of long-term clinical stability (61).

1.3.2 Fulminant myocarditis

The children with acute viral myocarditis comprise the group most likely to benefit from VAD insertion. Those children are usually healthy before the onset of fulminant myocarditis, therefore long-term mechanical circulatory support could be an effective option for bridging to myocardial recovery. Previously, Duncan et al. have reported ECMO or centrifugal pump treatment of 15 children with fulminant myocarditis, and the survival rate was 80% (22). However, the median support time of the children included in their study was only 6 days, and 5 patients received early cardiac transplantation. In combination with pharmacological treatment, mechanical circulatory support for a longer time with a VAD might lead to complete cardiac recovery in children

suffering from myocarditis, which has been seen after 1-3 week, and allows pump explantation. If cardiac function does not improve with VAD support for several months, heart transplantation must be considered (44, 62).

1.3.3 Post-cardiac surgery

Although the surgical techniques, the management of cardiopulmonary bypass, and myocardial protection have consistently improved in recent years, myocardial dysfunction can still occur after surgery in a portion of the children with complex congenital heart disease, resulting in failure of the left, right, or both ventricles. About 2-5% of pediatric patients who received open heart surgery need mechanical circulatory assistance. In almost all cases, mechanical circulatory assistance was used as rescue support, with a relatively low survival. The decision to use mechanical support after failed surgery should be made as soon as possible. The indication for use of mechanical support is poor myocardial function in conjunction with metabolic acidosis, oliguria, rising lactate level, low perfusion despite high-dose inotropic support, afterload reduction, and an optimal combination of pharmacologic agents. Intra-cardiac shunts should be closed before children receive mechanical circulatory devices implantation. It is also important to select the optimal mechanical device. If children were expected to recover within two weeks, their lung function is not harmed; a centrifugal pump may be the best choice. In children with concomitant respiratory failure, ECMO implantation should be considered. Long-term pulsatile VAD is the best option for children with no residual shunts but with a low probability of myocardial recovery. In our experience, the survival rate has significantly increased with the earlier decision for MCS implantation after failed surgery.

1.3.4 Chronic stages of congenital heart disease

Pediatric patients with chronic congenital heart disease may develop ventricular failure several years after operation. They become candidates for heart transplantation when all other surgical and medical therapies have been exhausted. As in pediatric patients with cardiomyopathy, VAD implantation as a bridge to transplantation should be considered for children with congenital heart disease, when heart transplantation is the only final option. The surgical procedure of VAD implantation could be more difficult than in other groups, since these children have complex anatomic disorders, and are much likely to have previous operations before VAD implantation (61).

2. Aim of the Study

For patients with intractable heart failure, cardiac transplantation has been the most effective long-term therapy. However, it is not unusual for a child listed as a heart transplant candidate to wait several months before an organ becomes available. In order to assist the failing heart in infants and small children, mechanical circulatory support with a variety of devices has been routinely applied in pediatric patients with end-stage heart disease, aiming at bridge to transplantation or myocardial recovery. Current options for mechanical support in children include miniaturized intraaortic balloon pumps, ECMO, centrifugal pumps, pulsatile VADs, and axial flow devices.

ECMO and centrifugal pumps remain the most common forms of mechanical support available, and are the best option for acute decompensation. ECMO can provide total cardiopulmonary support, is relatively rapid, and allows the flexibility of peripheral and central cannulation. ECMO pumps, however, produce nonpulsatile flow and the circuit is complex. The incidence of medium and long-term bleeding and infectious complications is exceedingly high and neurological impairment with extended use is also common (64). ECMO also restricts patient mobility, impairing physical rehabilitation (65-66).

Ventricular assist devices have potential advantages over ECMO and centrifugal pumps as a mechanical bridge. Pulsatile pumping results in better tissue perfusion and specifically provides better recruitment of the microcirculation of the brain, lungs, and kidneys during extracorporeal circulation. In addition to improving the patient's hemodynamic status and reversing end-organ dysfunction, VADs can be partially or fully implanted and allow for physical rehabilitation to improve the patient's overall condition and likelihood for successful transplantation.

Although several adult-sized ventricular assist devices could be implanted in larger adolescent patients, they could not provide circulatory support in small children with weight less than 20 kg (46, 67). Specific concerns regarding "oversized" devices have been documented. Pumping large stroke volumes into a small aorta can perpetuate systolic hypertension and subsequent intracranial hemorrhage, stasis in the device can cause thromboembolic complications, and placement of multiple adult size cannulae in a limited pericardial space can be technically challenging.

Current experience with the use of pediatric-specific VADs in children is limited, and previous studies were mostly based on either adult-sized VADs or a relatively small patient number (11, 68-78). Furthermore, for the pediatric population, classic guidelines for VAD implantation have not always been successful, since almost all of them were based on adult VAD patients, and these models might be largely unsubstantiated when applied to children (79).

Therefore, we conducted a retrospective analysis by collecting the data of the patients with age < 18 years who were supported by Berlin Heart EXCOR Pediatric VADs at DHZB between 1999 and 2009. The purposes of the study included: (1) describing the recent 10-year the Deutsches Herzzenturm Berlin (DHZB) experience with long-term mechanical circulatory support in small children and young adolescents with intractable heart failure; (2) for better understanding of patient selection and timing of VAD implantation in the pediatric end-stage heart failure population, and further definition of the preoperative risk factors for in-hospital mortality in children.

3. Patients and methods

3.1 Patients

Between January 1, 1999 and December 31, 2009, a total of 73 pediatric patients (< 18 years) were implanted with Berlin Heart EXCOR pediatric ventricular assist devices at DHZB. All these children had irreversible end-stage heart failure requiring inotropic support without any possibility of weaning from intravenous catecholamine administration, or failure of weaning from cardiopulmonary bypass after cardiac surgery, and a large proportion of them were moribund at the time of implantation.

3.2 Criteria for Berlin Heart EXCOR pediatric VAD implantation

Timing of device implantation and patient selection are of critical importance for improving outcomes in VAD recipients. The current criteria for pediatric VAD usage at DHZB are the following:

1. Rapid deterioration of the circulation;
2. Critical peripheral perfusion; metabolic acidosis;
3 Cardiac index < 2.0 L/min/m^2; mixed venous saturation < 40%;
4. Signs of beginning renal and hepatic failure;
5. Patient on respirator with mounting FiO2;
6. Massively impaired cardiac function as shown by echocardiography;
7. High or rapidly increasing B-type natriuretic peptide (BNP) or N-terminal proBNP level.

3.3 Surgical procedure for implantation of Berlin Heart EXCOR pediatric VAD

The operation is performed with cardiopulmonary bypass and mild hypothermia on the beating heart. We use short periods of fibrillatory or cardioplegic arrest only when closing the intracardiac shunts. The left inflow cannulation is introduced into the left ventricular apex, and

the left outflow cannulation is connected to the ascending aorta. Right atrial to main pulmonary artery cannulation was used for the right-sided device.

3.4 Postoperative management

Anticoagulation

Postoperative anticoagulation therapy is started 8 hours after surgery, with continuous heparin infusion (400 to 600 IU/kg) if there i8s no bleeding. We measure the activated partial thromboplastin time (PTT) every 4 to 6 hours in the first few days, and change to twice daily after stabilization, with a target range of 60 to 80 seconds. Thromboelastography is used to identify the coagulation status and impact of heparin. Antithrombin III is also closely monitored and substituted if the level falls below 70%. Since 2007, pediatric recipients have received low molecular weight heparin for long-term anticoagulation, and anti-Xa activity was evaluated in those patients, with a target range of 1.0 to 1.2 IU/ml. Patients received anti-aggregation (aspirin) and anti-adhesion (dipyridamole) drugs after the first week of support and removal of the chest drains, when the platelet count and the platelet function were normal. L-hirudin or argatroban was used for heparin-induced thrombocytopenia. In the late postoperative period, anti-vitamin K (coumadin) was given when the patient could feed orally.

Antibiotics

As a routine procedure, during the first week, pediatric patients receive a second-generation cephalosporin, and vancomycin is given to the children whose chests were left open. After the first week, antibiotics are given to those who have suspected or proved infections.

Blood loss

Oral ferritin and subcutaneous erythropoietin were given to children with up to 20 kg body weight, preventing red cell transfusions.

Mobilization, nutrition, dressings, and family support

A few hours after VAD operation, enteral nutrition could be started. Early extubation and mobilization are beneficial for recovery, and thus should be performed as soon as possible. For early detection of clots and films, careful inspection of the pumps and cannulas with a strong torch and a small mirror is needed and should be daily performed. Daily changing of the patient dressings is not necessary; when there is no bleeding or secretion, a specialized nurse changes the dressings twice a week, following the strict rule never to stick any tape on the pumps or on the cannulas to prevent clouding of the transparent material.

3.5 Weaning criteria

Weaning could be considered when patients have continuous improvement of myocardial function and appropriate changes in ventriclar wall thickness. For larger children, we measured pulmonary pressure with a pulmonary catheter, and for smaller patients, echocardiography was applied. Echocardiography without no dobutamine stress was performed. Next, we decreased the pump flow and carefully observed changes of blood pressure and ventricular filling. We performed echocardiographic evaluation (conventional echocardiography plus tissue Doppler and strain imaging) during pump stop lasting not more than 30 minutes. During echocardiographic evaluation, an additional dose of heparin should be administered (70-100 IU/kg), and we manually operated the pump system (1-2 times every 30 seconds) to avoid formation of thrombus. The decision to wean children from the VAD was made, if patients' left ventricular ejection fraction remained stable at > 45%, left ventricular end-diastolic diameter also remained stable at around the age-related 97% percentile of normal and, if appropriate, mitral valve regurgitation did not worsen during repeated pump stops (usually 3-4) without any inotropic support. In addition, during repeated pump stops, central venous saturation and pulmonary artery pressure (estimated by echocardiography) are considered as improtant prognostic indexes, as is the level of BNP or NT-proBNP during the whole weaning period. An additional biopsy should be performed in patients with suspected myocarditis or unclear diagnosis. The weaning protocol is the same for different pump sizes. Weaning is considered successful if children have stable cardiac function during the first year after ventricular assist device explantation.

3.6 Discharge home on Berlin Heart EXCOR pediatric VAD

Discharge home with VAD support is allowed in Germany. For older patients with the portable Berlin Heart Excor VAD driver, patients were discharged whenever possible. They received anticoagulation therapy with vitamin K antagonist (monitored with international normalized ratio (INR) measurement device) and acetylsalicylic acid (monitored by platelet aggregation tests performed at ambulatory visits). These patients can go to school with VAD support. Detailed information on the outpatient management has been reported (63). Small children who need the powerful, stationary IKUS driver and continuous heparin infusion (except patients treated with low-molecular heparin) are kept in hospital.

3.7 Data collection

We conducted a retrospective analysis of data obtained from the ventricular assist device registry database of DHZB. To identify the potential risk factors for in-hospital survival in pediatric patients with VAD support, subjects were categorized into two groups: children who survived during the first three-month hospitalization after VAD implantation (survivor group) and those who did not (non-survivor group). The following clinical data were collected and analyzed:

1. Patient characteristics: age, sex, BSA, body length, weight, body mass index, causes of heart failure, prior sternotomy, history of comorbidities, and year of EXCOR implantation;

2. Preoperative clinical events and medical interventions: preimplantation intensive care unit (ICU) stay, ventilator support, renal replacement therapy, cardiac pulmonary resuscitation (CPR), intravenous inotropes, vasopressor, vasodilators, diuretics, antiarrhythmic therapy, and mechanical circulatory support before EXCOR implantation;

3. Vital clinical signs and measures of hemodynamic severity of heart failure: temperature, blood pressure (systolic, diastolic, and mean), heart rate, rhythm, pulse oxygen saturation (SpO_2), central venous pressure (CVP), pulmonary artery pressure (systolic, diastolic, and mean), pulmonary capillary wedge pressure (PCWP), cardiac output and index, and left ventricular ejection fraction (LVEF);

4. Laboratory data (< 24 hours before EXCOR implantation): serum sodium concentration, serum potassium concentration, serum glucose concentration, hemoglobin, white blood count, hematocrit, platelet count, INR, PTT, alanine and aspartate aminotransferase activity (ALT and AST), lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), γ-glutamyl transpeptadase (GGT), total bilirubin, serum albumin, total protein, blood urea nitrogen (BUN), serum creatinine concentration, and C-reactive protein (CRP);

5. Clinical outcomes: duration of ventilation, period of ICU stay, duration of EXCOR support, causes of EXCOR explantation, cause of death, posttransplantation survival, and adverse events.

3.8 Follow-up

The study patients were followed up until heart transplantation, myocardial recovery, death on mechanical support, or day of the last observation on April 30, 2010.

3.9 Statistical analysis

3.9.1 Descriptive statistics

Data were analyzed with PASW Statistic 18 (SPSS for Windows Release 18.0, SPSS Inc). Qualitative variables were described by frequency distributions; and for continuous variables, means and SDs were calculated. Qualitative data were compared with the Fisher exact test for 2 × 2 tables or Pearson chi-square otherwise. For continuous data, between group comparisons were performed with the use of an independent-samples t-test or the Mann-Whitney U test for normal and non-normal data, respectively.

3.9.2 Survival analysis

Survival estimates were based on the Kaplan-Meier method and compared by log-rank statistics. Patient survival was calculated from the day of VAD implantation until death on mechanical support. All survival analyses on VAD support were censored at the time of heart transplantation, explanation following myocardial recovery, or day of the last observation on April 30, 2010.

3.9.3 Risk-factor analysis

All preimplantation clinical parameters were firstly entered in the univariable analysis. Stepwise forward multivariate logistic regression model analyses were subsequently performed on univariable predictors of postimplantation mortality. The cut-off values for continuous variables were selected from the highest quartile, median, or lowest quartile, depending on the cut-off value that by univariate analysis correlated with the end point at a significance level of $P < 0.1$. Risk factors that correlated with the end point by univariate analysis at a significance level of 0.1 were entered and allowed to stay in a stepwise multiple logistic regression models.

4. Results

4.1 Patient characteristics

The preimplantation demographic characteristics of patients are listed in Table 1. Thirty-seven girls and 36 boys were included in this study. At the time of EXCOR implantation, median age was 4 years (mean, 6.2 years; range, 12 days to 17 years), with 32 (43.8%) of the recipients aged ≤ 1 year. The median patient weight was 14 kg (mean 22.3 kg; range, 3.22 to 80 kg), and the mean body surface area (BSA) was 0.8 m^2 (median 0.6 m^2; range, 0.2 to 2 m^2).

4.2 Diagnoses before VAD implantation

Most of the included patients had dilative cardiomyopathy and endomyocardial fibrosis (n = 52, 71.2%). The next largest population was patients with decompensated congenital heart defects (n = 17, 23.3%). Acute graft failure was a reason for VAD implantation in two children in our series (2.7%). The other two (2.7%) children suffered from acute myocarditis. There were eight patients requiring VAD support immediately after cardiac surgery. The origin of the congenital heart disease included transposition of aorta (n = 6), complete atrial ventricular septal defect (n = 3), single ventricle (n = 2), Bland-White-Garland syndrome (n = 2), interrupted aortic arch (n = 1), Ebstein's anomaly (n = 1), hypoplastic left heart syndrome (n = 1), and atrial septal defect with patent ductus botalli and left ventricular tumor (n = 1).

4.3 Preoperative status

Most of the patients received preoperative intravenous inotropic support plus mechanical ventilation (79.5%). Before VAD insertion, 25 patients (34.2%) received previous sternotomy, 26 (35.6%) needed cardiopulmonary resuscitation because of cardiac shock, 11 patients (15.1%) had renal insufficiency requiring dilatation therapy, and 12 (16.4%) received temporary support from ECMO or a centrifugal pump as a bridge to EXCOR.

Table 1 Patient demographics and characteristics

No. of patients	73
Male gender, %	49.3
Age, median (range), y	4 (12 d-17 y)
Age groups, n (%), y	
0-5	39 (53.4)
5-10	11 (15.1)
10-15	16 (21.9)
> 15	7 (9.6)
Weight, median (range), kg	14 (3.2-80)
Body surface area, mean (range), m^2	0.8 (0.2-2)
Etiology of heart failure, n (%)	
Non-congenital heart disease	56 (76.7)
Cardiomyopathy	52 (71.2)
Acute myocarditis	2 (2.7)
Graft failure	2 (2.7)
Congenital heart disease	17 (23.3)
Status before implantation, n (%)	
Mechanical ventilation	58 (79.5)
Previous sternotomy	25 (34.2)
Cardiopulmonary resuscitation	26 (35.6)
Renal insufficiency	11 (15.1)
Bridge to EXCOR	12 (16.4)

4.4 Survival

Of the 73 patients, 49 (67.1%) survived during the mechanical support period. Thirty-three patients were bridged to heart transplantation, 14 received explantation following myocardial recovery, and the other 2 continued to receive support and were eligible for transplantation. The accurate rate of survival on VAD support was 80.3%±5% and 55.5%±7.5% at 30 days and 1 year after EXCOR implantation, respectively, as depicted in Figure 4.

4.5 Causes of death on device

Among 24 patients who died during EXCOR support, the main causes of death included multiple organ failure in 8 children (33.3%), stroke in 5 (20.8%), cardiac failure in 3 (12.5%), infection in 2 (8.3%), and respiratory failure in 2 (8.3%).

4.6 Discharge

Of the 73 children implanted with EXCOR VAD, 23 patients died before explanation, 2 were hospitalized on EXCOR support and waited for heart transplantation, and the remaining 48 patients (65.8%) could be discharged home.

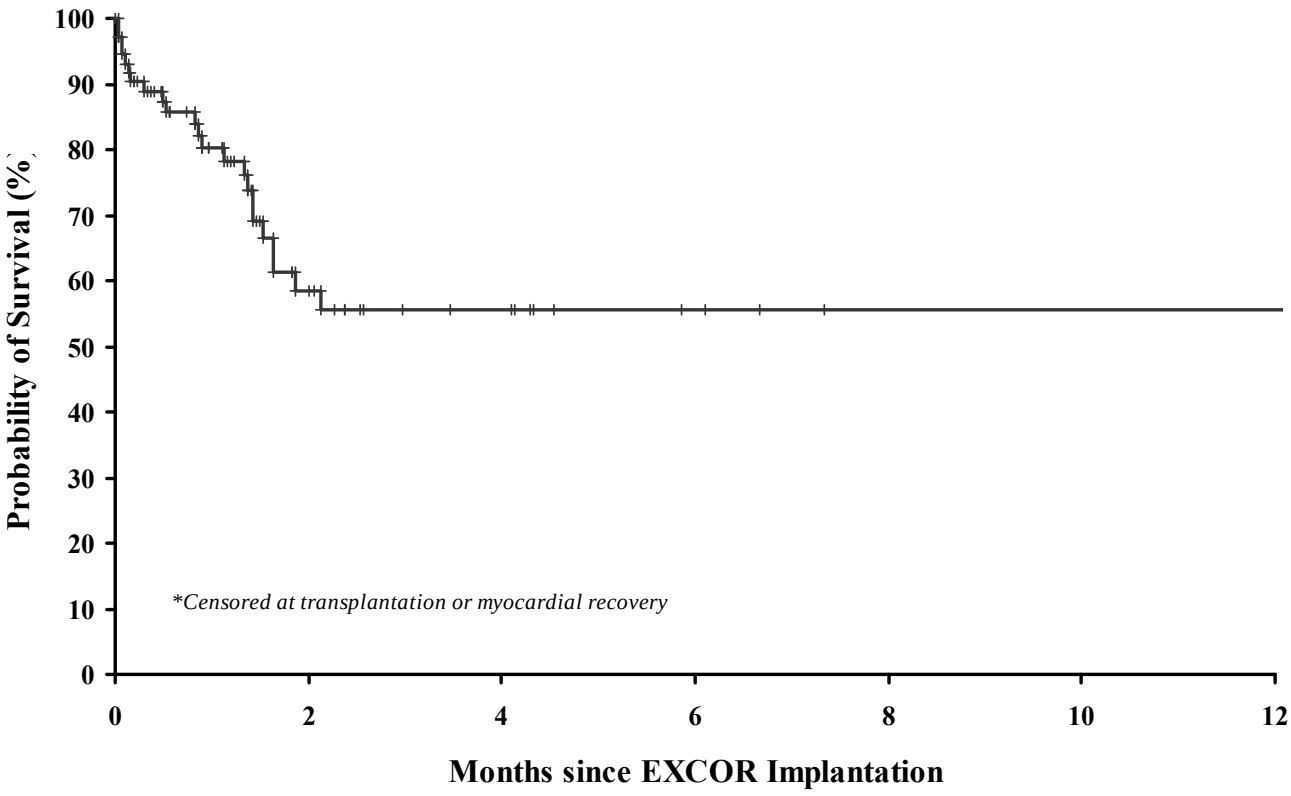

Figure 4 Kaplan-Meier analysis of survival in children supported with Berlin Heart EXCOR VAD

4.7 Morbidity

The overall mean length of EXCOR support was 59 days (median, 36 days; range, 1 to 432 days). The adverse events of pediatric patients after EXCOR implantation are summarized in Table 2. Major morbidities during EXCOR support included: infection in 33 patients (45.2%), stroke in 22 (30.1%), bleeding requiring reoperation in 20 (27.4%), pump exchange in 19 (26%), and renal failure in 17 (23.3%).

Table 2 Adverse events after EXCOR implantation

Adverse event	n (%)
Infection	33 (45.2)
Stroke	22 (30.1)
Bleeding requiring reoperation	20 (27.4)
Pump exchange	19 (26)
Renal failure	17 (23.3)

4.8 Subgroup analysis

4.8.1 Small children with BSA < 1.2 m^2

Of the 56 small children with BSA < 1.2 m^2 (mean, 0.56 m^2; range, 0.20 to 1.19 m^2), 15 patients were implanted with a BiVAD, and 41 received LVAD support (Table 3). The median age was 1 year (mean, 3.6 years, range, 12 days to 14 years), and the median weight was 8.75 kg (mean, 13.5 kg, range, 3.22 to 38 kg). Twenty-four patients were successfully bridged to transplantation, 12 were weaned from EXCOR support with cardiac recovery, 2 were still on support, and the other 18 children died after VAD implantation. The overall survival to transplantation, recovery of ventricular function, or ongoing device support was 67.9%, which was even slightly better than that of larger adolescents (64.7%). An additional analysis was done by only including children weighting < 20 kg, and a total of 31 (73.8%) of the 42 patients successfully survived during the support period. Morbidity after EXCOR implantation was also similar to that of adolescent patients, except that there was a higher incidence of stroke in small recipients, with 22 of the 56 small children (39.3%) experiencing a neurological event as compared to none of the 17 adolescent patients (0%) (P = 0.002).

Table 3 Small children (BSA < 1.2 m^2) versus larger adolescents (BSA ≥ 1.2 m^2): clinical course and adverse events

	Small children (n = 56)	Larger adolescents (n = 17)	P value
Age, median (range), y	1 (12 d-14 y)	15 (12-17)	< 0.001
Weight, median (range), kg	13.5 (3.2-38)	51.6 (30-80)	< 0.001
Body surface area, mean (range), m^2	0.42 (0.2-1.19)	1.57 (1.2-2.0)	< 0.001
Congenital heart disease, %	14 (25)	3 (17.6)	0.764
Clinical outcomes, n (%)			
Transplantation	24 (42.9)	9 (52.9)	0.464
Recovery	12 (21.4)	2 (11.8)	0.593
On-assist device	2 (3.6)	0 (0)	1.000
Death	18 (32.1)	6 (35.3)	0.809
Adverse events, n (%)			
Bleeding requiring reoperation	13 (23.2)	7 (41.2)	0.253

Infection	27 (48.2)	6 (35.3)	0.349
Pump exchange	17 (30.4)	2 (11.8)	0.225
Stroke	22 (39.3)	0 (0)	0.002
Renal failure	11 (19.6)	6 (35.3)	0.497

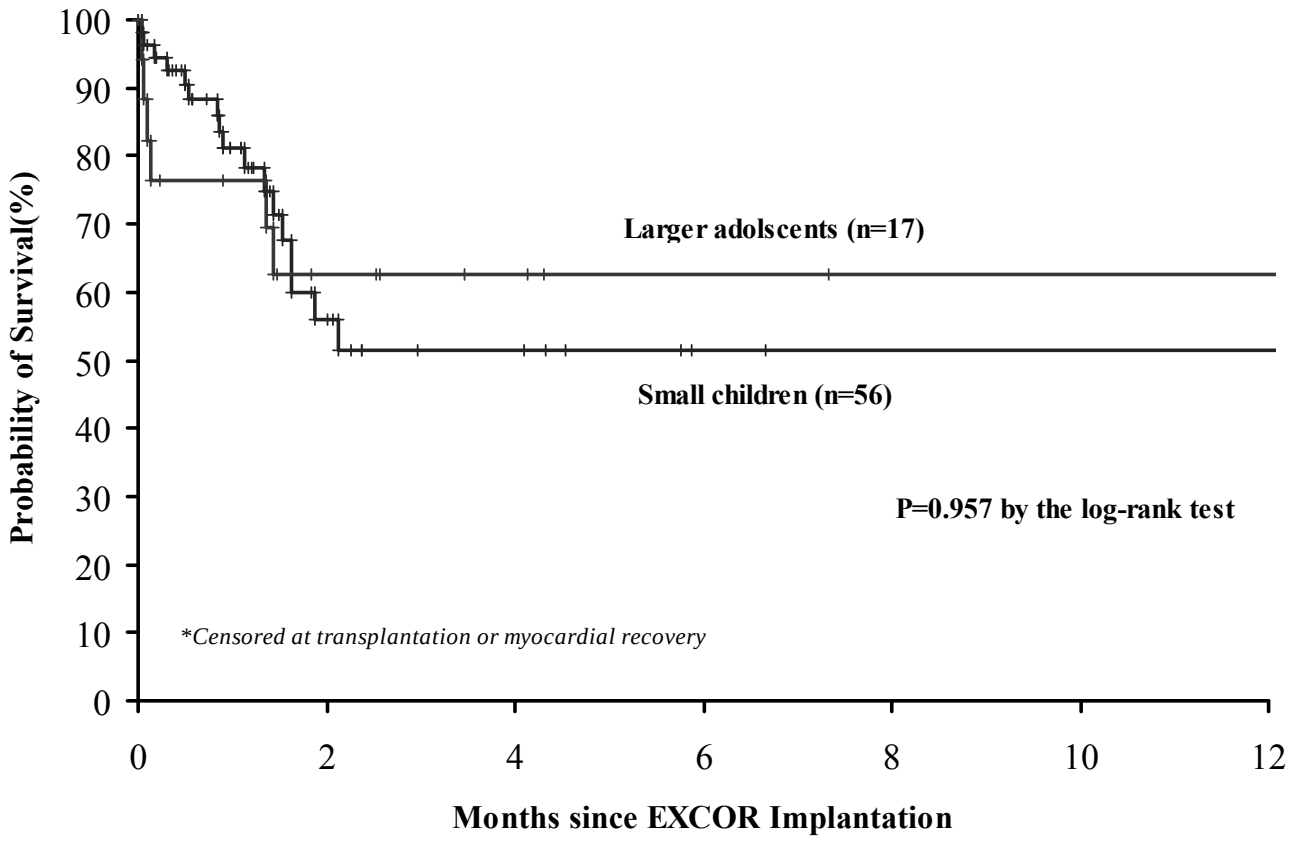

Figure 5 Kaplan-Meier analysis of survival in children supported with Berlin Heart EXCOR VAD: Small children versus Large adolescents

4.8.2 BiVAD versus Univentricular assist device (UniVAD)

In our study, 20 patients received biventricular support with BiVAD, 52 with LVAD, and the other 1 was supported with RVAD because of severe right heart failure (Table 4). Eleven of the 20 BiVAD patients died before VAD explanation (55%) compared with 13 of the 53 UniVAD recipients (24.5%) ($p = 0.01$). Overall actuarial survival for children receiving UniVAD and BiVAD implantation is depicted in Figure 6. Thirty-day and 1-year survival was 84.4%±5.5% and 66.3%±8.4% for UniVAD implantation, respectively; and 69.2%±10.5% and 33.6%±12.5% for children requiring biventricular support. Compared with patients supported with BiVAD, UniVAD recipients had significantly better survival ($p = 0.02$). There were no significant differences in the incidence of adverse events or causes of death for children implanted with UniVAD and those with BiVAD implantation.

Table 4 BiVAD versus UniVAD: clinical course and adverse events

	BiVAD (n = 20)	UniVAD (n = 53)	P value
Age, median (range), y	8.5 (0.33-17)	2 (12 d-17 y)	0.234
Weight, median (range), kg	24 (5.5-80)	10 (3.2-58.5)	0.105
Body surface area, mean (range), m^2	0.95 (0.29-2)	0.73 (0.2-1.7)	0.107
Congenital heart disease, %	5 (25)	12 (22.6)	1.000
Clinical outcomes, n (%)			
Transplantation	8 (40)	25 (47.2)	0.583
Recovery	1 (5)	13 (24.5)	0.120
On-assist device	0 (0)	2 (3.8)	0.939
Death	11 (55)	13 (24.5)	0.013
Adverse events, n (%)			
Bleeding requiring reoperation	7 (35)	13 (24.5)	0.371
Infection	8 (40)	25 (47.2)	0583
Pump exchange	5 (25)	14 (26.4)	0.902
Stroke	6 (30)	16 (30.2)	0.987
Renal failure	7 (35)	10 (18.9)	0.253

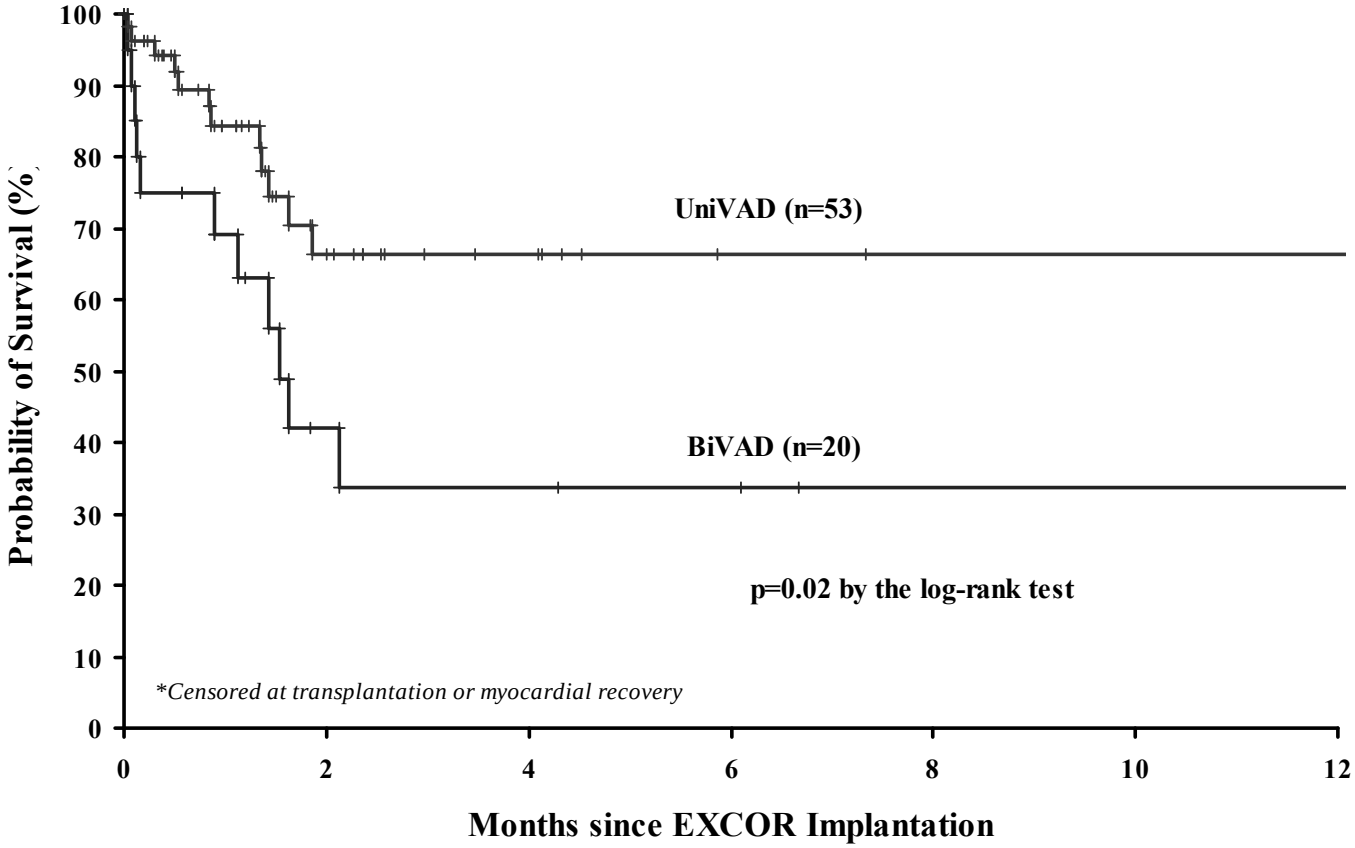

Figure 6 Kaplan-Meier analysis of survival in children supported with Berlin Heart EXCOR VAD: BiVAD versus UniVAD

4.8.3 Patients listed for transplantation

52 children implanted with EXCOR were listed for heart transplantation, and 40 of them (76.9%) survived to transplantation (n = 33), recovery of ventricular function (n = 5), or continued support (n = 2) (Table 5). The accurate survival rate on EXCOR support was 88.3%±4.9% and 68.4%±8.2% at 30 days and 1 year after EXCOR implantation, respectively (Figure 7). Of the 33 patients who were successfully bridged to heart transplantation, the accurate survival rate at 5 years after transplantation was 90.1%±5.5%.

Table 5 Patients listed for transplantation: clinical course and adverse events

	Listed for transplantation (n = 52)
Age, median (range), y	3.5 (12 d-17 y)
Weight, median (range), kg	13.6 (4.1-70.5)
Body surface area, mean (range), m^2	0.76 (0.24-1.9)
Congenital heart disease, %	6 (42.9)
Clinical outcomes, n (%)	
Transplantation	33 (63.5)
Recovery	5 (9.6)
On-assist device	2 (3.8)
Death	12 (23.1)
Adverse events, n (%)	
Bleeding requiring reoperation	14 (26.9)
Infection	24 (46.2)
Pump exchange	19 (36.5)
Stroke	17 (32.7)
Renal failure	8 (15.4)

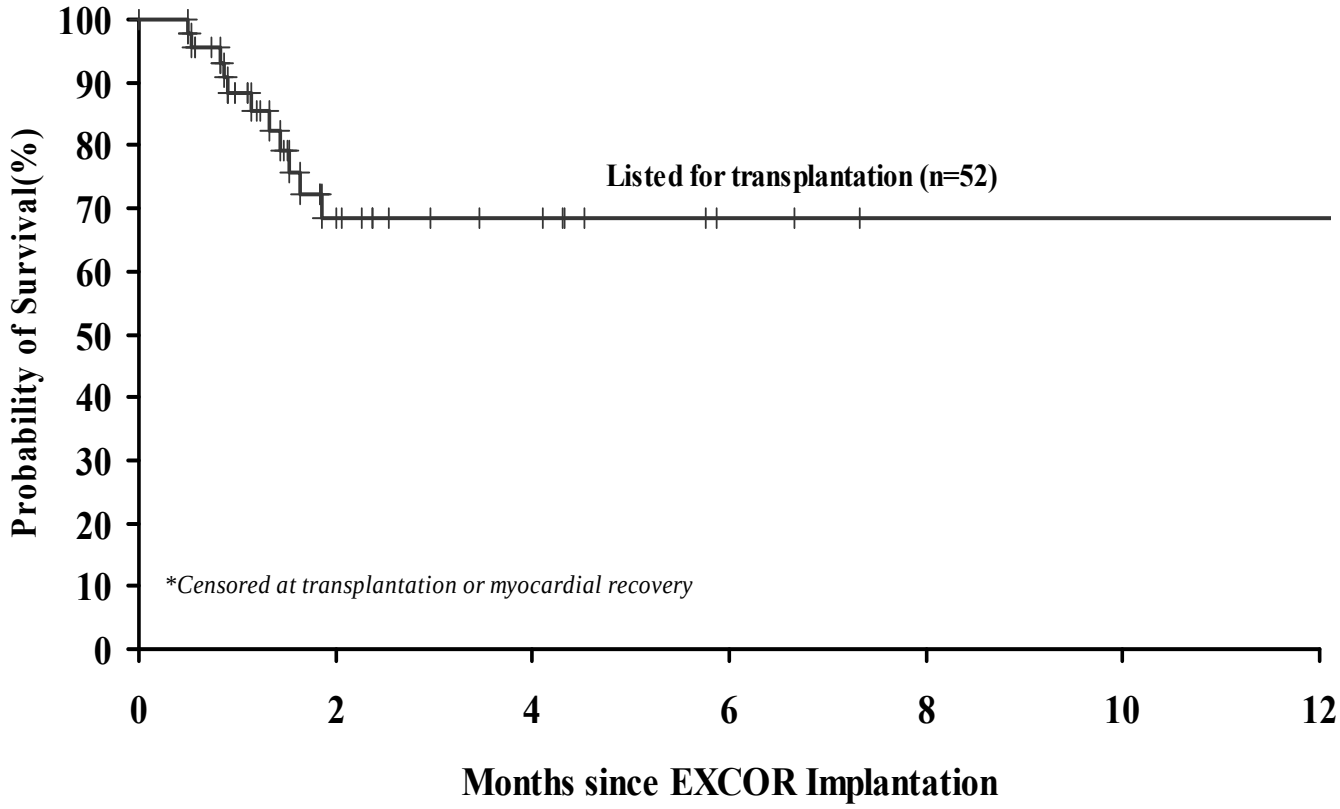

Figure 7 Kaplan-Meier analysis of survival in children listed for transplantation

4.8.4 Children with congenital heart disease

Of the 17 children with decompensated congenital heart defects, only 1 patient was successfully bridged to transplantation, 4 were weaned from EXCOR support with cardiac recovery, 1 was still on support, and the other 11 children died after VAD implantation (Table 6). The overall survival to transplantation, recovery of ventricular function, or ongoing device support was 35.3%. The Kaplan-Meier analysis showed significantly higher mortality in patients with congenital cardiac disease, as compared to children with non-congenital diagnosis ($p < 0.0001$) (Figure 8).

Table 6 Children with congenital heart disease versus patients with non-congenital diagnosis: clinical course and adverse events

	Non-congenital (n = 56)	Congenital (n = 17)	P value
Age, median (range), y	6.5 (12d-17y)	1 (12 d-17 y)	0.307
Weight, median (range), kg	18.5 (3.6-80)	9 (3.2-54)	0.226
Body surface area, mean (range), m^2	0.83 (0.22-2)	0.41 (0.2-1.7)	0.241
Clinical outcomes, n (%)			
Transplantation	32 (57.1)	1 (5.9)	< 0.0001
Recovery	10 (17.9)	4 (23.5)	0.866
On-assist device	1 (1.8)	1 (5.9)	0.954
Death	13 (23.2)	11 (64.7)	0.001
Adverse events, n (%)			
Bleeding requiring reoperation	14 (25)	6 (35.3)	0.601
Infection	24 (42.9)	9 (52.9)	0.464
Pump exchange	18 (32.1)	1 (5.9)	0.065
Stroke	16 (28.6)	6 (35.3)	0.597
Renal failure	14 (25)	3 (17.6)	0.764

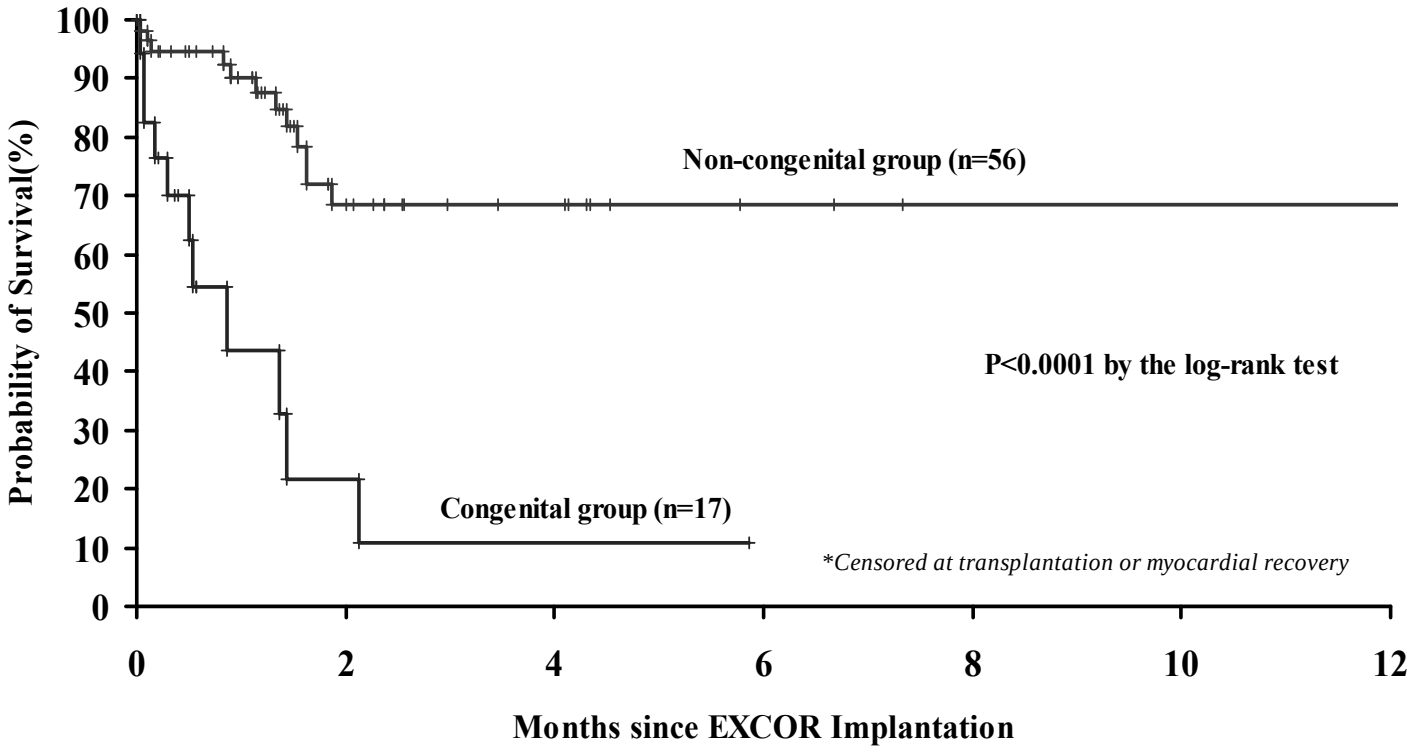

Figure 8 Kaplan-Meier analysis of survival in children with congenital heart disease

4.8.5 Bridge to Berlin Heart EXCOR VAD

Nine patients were supported by ECMO and 3 children were implanted with centrifugal pumps, as a bridge to EXCOR. Three were bridged to heart transplantation, 4 of them were weaned from VAD support with myocardial recovery, 1 remained supported, and 4 died during EXCOR support (Table 7). The overall survival to transplant, recovery, or ongoing support was 66.7%.

Table 7 Children with preimplantation mechanical support: clinical course and adverse events

	Bridge to EXCOR (n = 12)
Age, median (range), y	0.84 (12 d-16 y)
Weight, median (range), kg	8.3 (3.2-55)
Body surface area, mean (range), m^2	0.68 (0.2-1.6)
Congenital heart disease, %	4 (33.3)
Clinical outcomes, n (%)	
Transplantation	3 (25)
Recovery	4 (33.3)
On-assist device	1 (8.3)
Death	4 (33.3)
Adverse events, n (%)	
Bleeding requiring reoperation	4 (33.3)
Infection	6 (50)
Pump exchange	2 (16.7)
Stroke	5 (41.7)
Renal failure	4 (33.3)

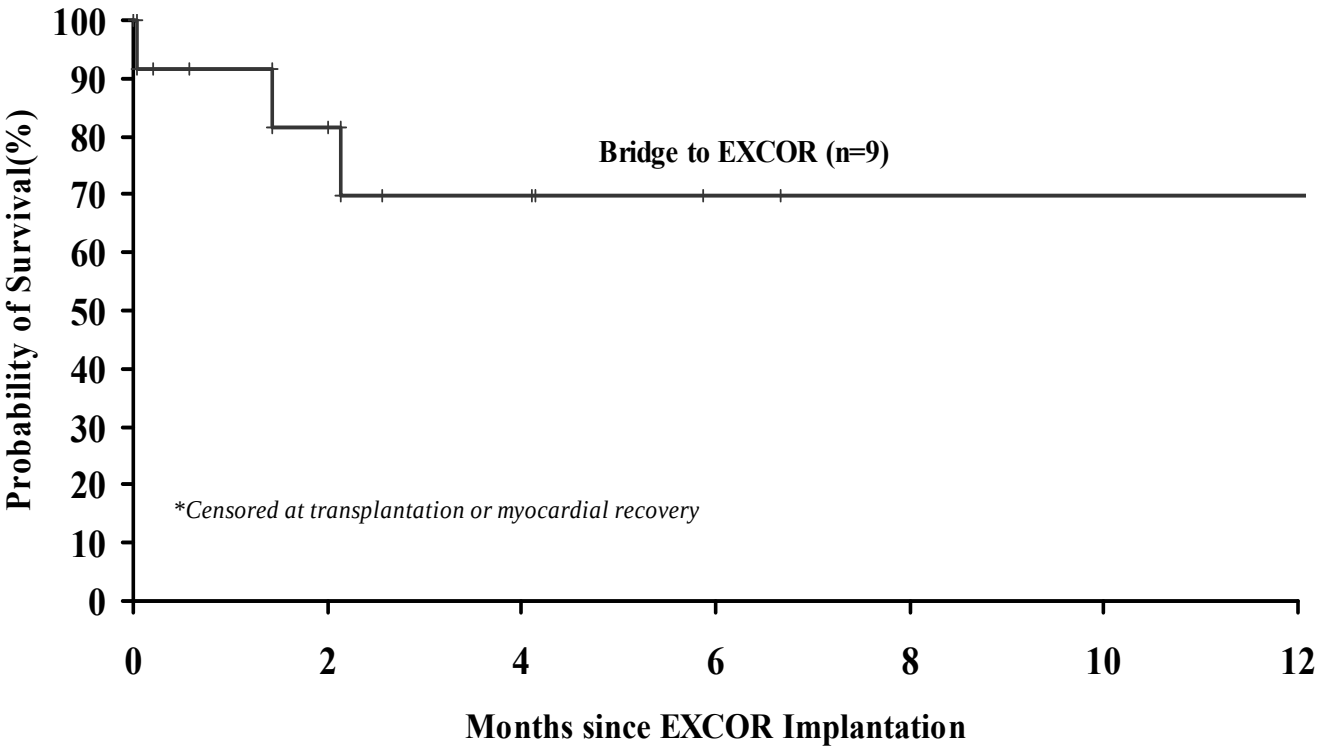

Figure 9 Kaplan-Meier analysis of survival in children with preimplantation mechanical support

4.9 Case report

Case 1

A previously healthy, 1 year-old girl had an acute infection in the upper respiratory tract, associated with deteriorating pulmonary function. The girl was diagnosed of dilative cardiomyopathy, and was immediately intubated. Thereafter, the girl presented a servere low-output syndrome and subsequent multi-organ failure. She was transferred to our hospital for an urgent ventricular assist device implantation. Shortly after she arrived, the blood pressure has dropped to 64/43 mmHg, and the heart frequency is 158 beat / minute. Laboratory test demonstrated impaired hepatic and renal functions. An echocardiograph was obtained, which showed that the ejection fraction was 10%. Thus, a left ventricular assist device (Berlin Heart Excor VAD) was implanted. The postoperative process was quite stable, although she required sildenafil and NO therapies because of the higher pulmonary vessel resistance. 1 month after ventricular assist device implantation, the echocardiograph exam showed that her left ventricular function was significantly improved. During 20 minutes pump-stop test, her cardiac function remained stabile with systolic blood pressure > 90 mmHg. Therefore she was successfully weaned from VAD support, and discharged 2 weeks later.

Case 2

A 1-year old boy was diagnosed with Bland-White-Garland syndrome. With the deteriorating cardiac and pulmonary function, he was intubated and urgently transferred to our hospital. When arrived, he was connected to a respirator and was dystrophic. 3 days later, after cardiac function stabilized, he received a corrective surgery by re-implantation of the left coronary artery to the aorta root. However, this patient could not wean from cardiopulmonary bypass, and was soon implanted with a ventricular assist device. Postoperatively, his left ventricle was perfectly unloaded, and the left atrial pressure was maintained between 6 to 8 mmHg. The pump functioned well without any problem. The patient did not require any inotropic support. On the 9th day after surgery, we reduced the pump frequency to 50%, and the echocardiograph examation showed cardiac function was greatly improved, without dilatation of the ventricle. Therefore, on the 12th day, the child was successfully weaned from VAD support. He received miliron and catecholamine administration, and his cardiac function remained good. The

echocardiographic examination demonstrated that the ejection fraction was 35%. This patient was discharged 2 days after weaned from Berlin Heart Excor VAD.

Case 3

This is a 14-year old girl diagnosed of Fallot Tetralogy, who has previously received several times of corrective surgeries, including Blalock-Taussig shunt, pulmonary valvotomy, closure of septum defect, and reconstruction of right ventricular outflow tract. Postoperatively implantation of a VVI-pacemaker was required because of AV-Block III. 1 year later, she received another corrective operation by insertion of a pulmonary artery homograft (with pulmonary valve). 8 years later, she had an acute myocardial decompensation with ventricular tachycardia, needing acute cardiopulmonary reanimation. She was intubated and supported with mechanical ventilation immediately. Because of the continuous deterioration of ventricular function, she was implanted with a biventricular assist device (Berlin Hear EXCOR VAD), and urgently listed for heart transplantation. 3 months after Berlin Hear EXCOR VAD implanted, she luckily received a suitable cardiac donor, and the transplantation procedure was very successful. Postoperatively, her circulatory statue was stable, and she was extubated on the first day after operation. The girl was discharged 1 month later.

Case 4

A 4-month old girl was diagnosed with complete atrioventricular septum defect, and she received a corrective surgery in another hospital. However, there was a serious postoperative complication (myocardial bleeding on the left ventricle), and she presented an acute low-output syndrome. She was immediately implanted with an ECMO. After failing several times to try to wean from ECMO support, this patient was urgently transferred to our center, for implantation of a ventricular assist device as bridge to transplantation.

When the child arrived, she had seriuos low cardiac output and was supported with a ECMO. She was directly sent to our operation room to explant the ECMO, and further implant a ventricular assist device (Berlin Heart EXCOR VAD). The postoperative process was stable and problem less. She was listed for cardiac transplantation, and finally received a suitable pediatric heart donor 2 months after VAD implantation. She was discharged 1 month after the successful cardiac transplantation.

4.10 Risk factor analysis

4.10.1 Baseline preoperative clinical demographics

The preoperative recipient demographics, associated odds ratios (OR), and 95% confidence interval (CI) for univariable predictors of death with a $p < 0.1$ are shown in Table 8. Congenital diagnosis and a prior sternotomy were the only demographic predictors of mortality after EXCOR implantation in small children. Of note, none of the age-dependent indexes were risk factors for death after VAD surgery.

Table 8 Baseline patient demographics

	Survival (n = 50)	Non-survival (n = 23)	P Value	Odds Ratio (95 CI)
Age, years	5.64±6.17	7.45±6.02	0.246	
Sex				
male	22	14	0.180	
female	28	9		
Weight, kg	20.9±18.89	25.52±20.49	0.237	
BSA, m^2	0.75±0.51	0.90±0.52	0.163	
BL, cm	103.4±43.13	117.76±41.16	0.128	
BMI, kg/m^2	15.24±2.85	15.32±3.42	0.918	
Etiology for heart failure			0.001	6.72 (2.06-21.92)
Congenital disease	6	11		
Non-congenital disease	44	12		
Prior sternotomy (+)	12	13	0.007	4.12 (1.44-11.76)
Prior sternotomy (-)	38	10		
Implantation year ≥ 2004	37	15	0.441	
Implantation year < 2004	13	8		

Odds ratios are shown for univariable predictors with $p < 0.1$.

*p value for between-group comparisons.

(+) = condition present; (-) = condition absent; BMI = body mass index; BSA = body surface area; CI = confidence interval; BL = body length.

4.10.2 Preoperative clinical events and medical interventions

Table 9 lists the pre-operative events and medical interventions that occurred in children supported with EXCOR. There were no differences in preoperative ICU stay, length of preoperative ICU stay, and time on ventilator support between the survival and non-survival groups. Additionally, use of preimplantation mechanical support as a bridge to EXCOR, preimplantation ventilation support, CPR, and renal replacement therapy were also not associated with survival in children after EXCOR implantation.

Table 9 Preoperative clinical events and medical interventions

	Survival (n = 50)	Non-survival (n = 23)	P Value	Odds ratio (95 CI)
Preoperative ICU stay (+)	47	22	1.000	
Preoperative ICU stay (-)	3	1		
Length of pre-operative ICU stay, hours	76.34±109.67	141.36±184.22	0.146	
Bridge to VAD			0.805	
None	41	20		
ECMO	7	2		
Centrifugal Pump	2	1		
Ventilator support (+)	37	21	0.123	
Ventilator support (-)	13	2		
Time on ventilator support, hours	66.27±91.05	102.53±176.14	0.410	
Renal replacement therapy (+)	6	5	0.306	
Renal replacement therapy (-)	44	18		
CPR (+)	16	10	0.341	
CPR (-)	34	13		

Odds ratios are shown for univariable predictors with $p < 0.1$.

*p value for between-group comparisons.

(+) = condition present; (-) = condition absent; CI = confidence interval; ICU = intensive care unit; ECMO = extracorporeal membrane oxygenation; CPR = cardiopulmonary resuscitation.

4.10.3 Preoperative intravenous medications

Table 10 shows the pre-operative intravenous medication given in the EXCOR sample. Requirements for a vassopressor and norepinephrine were associated with higher mortality after EXCOR implantation. Use of inotropic agents, vasodilator, diuretics, and antiarrhythmic drugs were not predictors of post-VAD survival.

Table 10 Preoperative intravenous medication requirements

	Survival (n = 49)	Non-survival (n = 21)	P Value	Odds ratio (95 CI)
Inotrope				
Inotrope > 1 (+)	24	10	0.917	
Inotrope > 1 (-)	25	11		
Inotrope > 2 (+)	12	2	0.202	
Inotrope > 2 (-)	37	19		
Milrinone (+)	38	13	0.177	
Milrinone (-)	11	8		
Dobutamine (+)	15	4	0.319	
Dobutamine (-)	34	17		
Dopamine (+)	18	7	0.785	
Dopamine (-)	31	14		
Vasoactive agents				
Vasopressor (+)	32	18	0.083	3.19 (0.82-12.38)
Vasopressor (-)	17	3		
Epinephrine (+)	32	16	0.369	
Epinephrine (-)	17	5		
Norepinephrine (+)	3	6	0.018	6.13 (1.36-27.58)
Norepinephrine (-)	46	15		
Vasodilator (+)	17	8	0.785	
Vasodilator (-)	32	13		
Diuretics				
Diuretics (+)	38	18	1.000	
Diuretics (-)	11	3		

Antiarrhythmic therapy			
Antiarrhythmic drug (+)	10	3	0.529
Antiarrhythmic drug (-)	39	18	
Amiodarone (+)	7	3	1.000
Amiodarone (-)	42	18	

Odds ratios are shown for univariable predictors with $p < 0.1$.

*p value for between-group comparisons.

(+) = condition present; (-) = condition absent; CI = confidence interval.

4.10.4 Preoperative echocardiography and cardiopulmonary hemodynamic measurements

In Table 11, preoperative echocardiographic and hemodynamic data are presented. Patients with higher CVP, or higher pulmonary artery systolic, diastolic, and mean pressures were more likely to die after EXCOR implantation. When evaluated categorically, a CVP > 17 mm Hg was predictive of post-VAD mortality.

Table 11 Preoperative echocardiographic and cardiopulmonary hemodynamic measurements

	Survival (n = 50)	Non-survival (n = 23)	P Value	Odds ratio (95 CI)
Vital signs				
Temperature, °C	36.63±1.42	36.99±2.18	0.420	
Systolic blood pressure, mmHg	78.92±18.02	75.10±19.93	0.434	
Diastolic blood pressure, mmHg	50.8±11.96	47.81±9.94	0.319	
Mean arterial pressure, mmHg	59.98±12.82	57.52±11.15	0.448	
CVP, mmHg	12.08±6.05	16.14±7.15	0.018	
CVP > 17 mmHg	7	8	0.054	3.60 (1.10-11.86)
CVP ≤ 17 mmHg	41	13		
Heart rate, beats/min	125.59±30.09	124.29±36.12	0.876	
SpO_2 (%)	97.12±3.98	93.62±11.90	0.501	
Cardiopulmonary hemodynamics				
Mean PA pressure, mm Hg	32.94±12.51	25.60±12.18	0.099	
PA systolic pressure, mm Hg	46.06±15.34	34.60±14.98	0.039	
PA diastolic pressure, mm Hg	25.83±9.99	19.13±10.72	0.073	
Pulmonary capillary wedge pressure, mmHg	22.83±9.1	23.06±13.22	0.961	
Cardiac output, l	6.250±8.797	4.981±5.119	0.768	
Cardiac index, l/min/m^2	7.397±10.036	2.712±1.094	0.122	
LVEF, %	25.00±16.51	21.63±8.38	0.962	

Odds ratios are shown for univariable predictors with $p < 0.1$.

*p value for between-group comparisons.

CI = confidence interval; CVP = central venous pressure; SpO_2 = pulse oxygen saturation; PA = pulmonary artery; LVEF = left ventricular ejection fraction.

4.10.5 Preoperative laboratory measurements.

Table 12 gives the results of pre-operative blood results. There were increased odds of mortality in patients with higher preoperative BUN and CRP. When evaluated categorically, C-reactive protein > 4.96 mg/dl, blood urea nitrogen > 74 mg/dl were predictive of in-hospital mortality in children after EXCOR implantation.

Table 12 Preoperative laboratory values

	Survival (n = 50)	Non-survival (n = 23)	P Value	Odds ratio (95 CI)
Sodium, mmol/l	136.39±7.65	137.54±5.74	0.550	
Potassium, mmol/l	4.23±0.73	4.16±0.56	0.711	
Glucose, mg/dl	157.43±90.04	157.21±63.76	0.671	
Hemoglobin, g/dl	11.93±1.87	11.58±1.58	0.448	
Hemocrit, %	34.85±5.96	33.58±5.37	0.399	
White blood cell count, k/mm^3	12.49±6.57	13.19±6.10	0.674	
Platelets, k/mm^3	240.54±117.29	212.66±151.53	0.451	
INR	1.72±0.95	1.82±0.95	0.343	
PTT, s	73.52±70.02	70.38±57.06	0.989	
GPT, IU/l	187.88±389.10	89.73±163.58	0.339	
GOT, IU/l	343.49±719.63	215.06±370.77	0.955	
LDH, IU/l	730.11±861.42	780.85±1177.16	0.468	
CK-MB, IU/l	58.78±93.22	89.50±168.72	0.343	
GGT, IU/l	49.35±36.71	58.86±76.06	0.190	
Total bilirubin, mg/dl	1.24±1.34	3.84±5.78	0.119	
BUN, mg/dl	50.70±34.60	74.51±50.80	0.061	
BUN > 74 mg/dl	8	8	0.065	2.92 (0.91-9.37)
BUN ≤ 74 mg/dl	38	13		
Creatinine, mg/dl	0.93±0.80	1.15±0.91	0.335	
TP, g/l	5.93±1.27	5.43±0.94	0.116	
Albumin, g/dl	3.16±0.61	2.94±0.58	0.174	

CRP, mg/dl	2.84±4.25	5.11±5.77	0.065	
CRP > 4.96 mg/dl	6	7	0.065	3.11 (0.90-10.77)
CRP ≤ 4.96 mg/dl	40	15		

Odds ratios are shown for univariable predictors with $p < 0.1$.

*p value for between-group comparisons.

CI = confidence interval; INR = International normalized ratio; PTT = partial thromboplastin time; GPT = glutamate pyruvate transaminase; GOT = glutamic oxaloacetic transaminase; LDH = lactate dehydrogenase; CK-MB = creatine kinase-MB; GGT = γ-glutamyl transpeptadase; BUN = blood urea nitrogen; TP = total protein; CRP = C-reactive protein

4.10.6 Multivariate analysis

Clinical, echocardiographic, laboratory, and hemodynamic variables with a univariable $p < 0.1$ for predicting mortality after EXCOR implantation were entered into the multivariable logistic regression analyses. Remaining independent predictors of mortality after EXCOR implantation included a congenital diagnosis (P = 0.001, OR 11.34, 95% CI 2.73 to 47.03), and CVP > 17 mmHg (P = 0.039, OR 4.24, 95% CI 1.08 to 16.67). The Hosmer and Lemeshow test showed that this model provided moderate fit with the data (P = 0.69). The multicollinearity analysis indicated that our risk factors were not confounded by the multicollinearity between these parameters.

The present analysis included both young children and adolescents, and patients with severe right heart failure requiring biventricular support and those who did not. In addition, the study period spans almost 14 years, during which significant improvement in the field of pediatric mechanical circulatory support has been achieved, which might also cause potential bias to our analysis. We assessed the possible confounding by these factors in logistic regression models that included each of these covariates (age at VAD insertion, biventricular support, and implantation year). All of the identified risk factors in our final regression model remained statistically significant after adjustment for these variables.

4.10.7 Survival analysis based on different risk groups

On the basis of this analysis, we further divided the recipient population into 2 subgroups: low-risk group which consisted of patients without any of the risk factors, and high-risk group that comprised children with at least 1 of the risk factors. The Kaplan-Meier estimate of actuarial survival was significantly better for low-risk recipients as compared to those from the high-risk group ($P < 0.0001$) (Figure 10). Estimates of the 30-day and 1-year survival rates were 92.2%±4.4% and 62.3%±9.7%, respectively, for the low-risk patients, and 75.9%±8.3% and 29.7%±10.4% for the high-risk candidates.

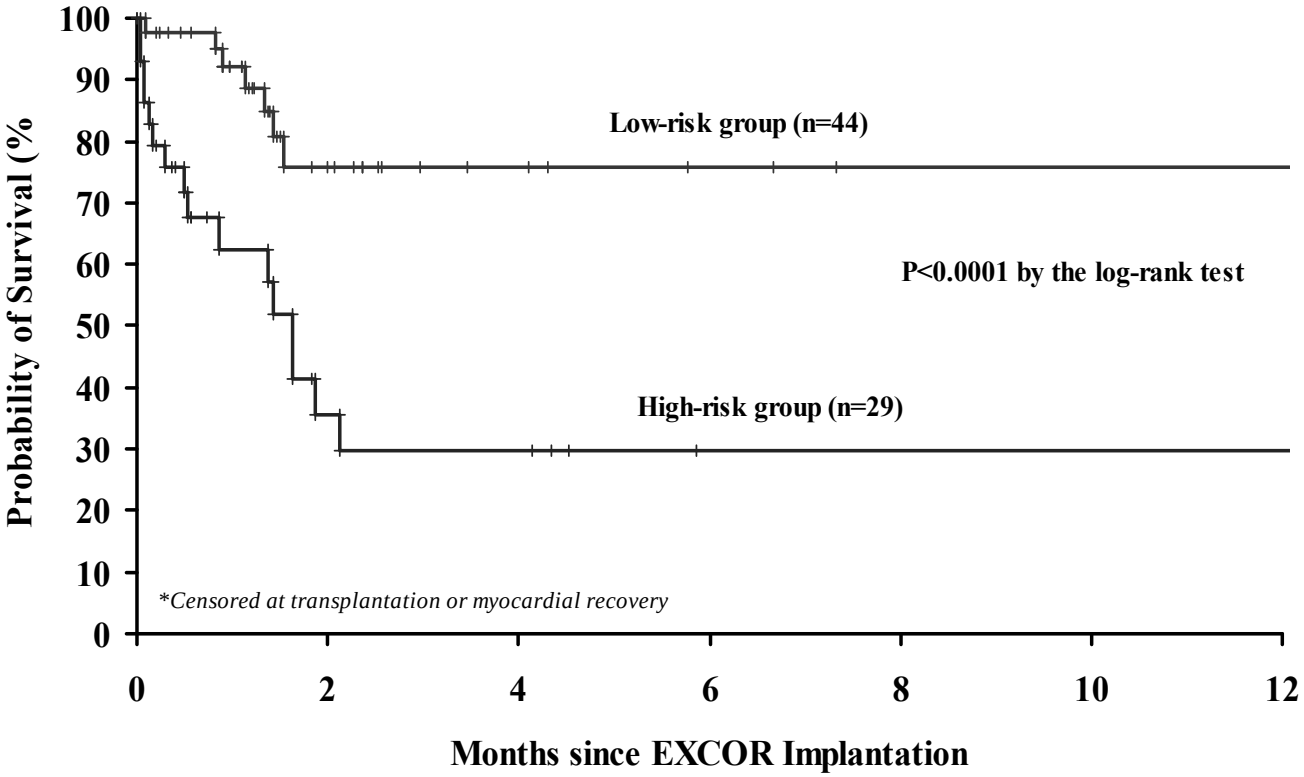

Figure 10 Kaplan-Meier analysis of survival in Children: High-risk group versus Low-risk group

5. Discussion

Despite considerable advances in medical therapy of severe myocardial failure, a subset of patients experiences progressive heart failure that finally becomes refractory to current treatment. For children with end-stage heart disease, cardiac transplantation provides the greatest survival benefit; however, infants and small children with lethal cardiac disease often die before transplantation because of the scarcity of suitable pediatric donor hearts (80-81). Shortage of donors remains the main limitation, and is the major cause of death for patients on the waiting list. Different with adult heart transplantation, many pediatric donor organs remain unused because there are no recipients of appropriate size with compatible blood types on the day of offer. With the prolonged waiting time, the requirement for long-term mechanical circulatory support in children has continuously increased since the past decade. Children with intractable heart failure who received mechanical assist device support do not die within hours, but get the chance to be bridged to transplantation for a period of weeks or months. With mechanical assist device support, mortality of pediatric patients waiting for heart transplantation can be significantly decreased, and exploitation of the pediatric-sized donor organs optimized.

For supporting the failing heart in children, ECMO (82-87) and centrifugal pumps (35) which are modifications of the original “heart-lung machine” circuit, have been used since the development of pediatric cardiac surgery, and are now still the mainstays in the field of pediatric mechanical circulatory support. ECMO could provide full cardiac and respiratory support in a rapid and simple manner, which is particularly effective for patients with acute decompensation. However, ECMO and centrifugal pumps are largely limited to lack of morbidity, the need for continuous intensive care, and the unsuitability for prolonged mechanical support. Bartlett et al. have reported their results of ECMO support in 13 moribund infants with respiratory failure who had undergone repair of congenital heart disease in 1976 (85). In 1989, in order to study the clinical use of ECMO and to maintain a registry, the Extracorporeal Life Support Organization was founded, and it has collected data on > 30,000 patients, most of whom were neonates with respiratory failure (86). Up to July 2004, 2215 neonates and 2936 children over 28 days old have undergone ECMO for cardiac indications, yielding survival rates to discharge home or transfer back to the non-ECMO center of 38% and 43% respectively.

Long-term VADs or "VADs" are either extracorporeal or implantable pneumatically or electrically driven systems with a variety of designs and functional principles. Adult patients are allowed to be discharged home with VAD support. Most of them could have a nearly normal life except for the requirement of an external power source; however, this is usually portable. Ventricular assist device is a well established therapy for patients suffered with end-stage heart disease, either as a bridge to transplantation, or comparatively rarely myocardial recovery. For adult patients who have no indications for heart transplantation, VADs could also be implanted as a permanent solution, and some of the recipients have been supported for longer than five years (90-95).

Ventricular assist devices have two major categories: pulsatile and continuous flow devices. The pulsatile devices drain back and eject out the blood with compressed air power (pneumatically driven) or electromechanical power. There are two valves in the artificial ventricle, either mechanical or biological. The current implantable rotary blood pumps available are axial or centrifugal flow pumps. This kind of pump has only one rotating part without valves. The majority of these devices are implanted for left ventricle support, but some of them could be used for assisting the falling right heart or both sides. Total artificial hearts are also available, which completely replace the native heart; and for these patients, transplantation is the only final option.

In comparison to centrifugal pumps and ECMO, ventricular assist devices have several inherent advantages. A VAD allows patients to be extubated, early mobilized, and fed orally, which optimizes patients' condition during the support period, and is advantageous when waiting periods of more than three or four weeks must be anticipated (96). VAD directly decompresses the left ventricle and provides pulsatile blood flow, which could restore end-organ function and decrease capillary leak. Furthermore, patients supported with VAD are much easier to transport, and require less anticoagulation and consumption of blood products that consequently reduce the associated risk of infection and HLA antibodies developing following transfusion (97-99).

Nevertheless, although mechanical support with VAD has been widely used in adult patients with end-stage heart disease, application of VAD in infants and small children is rarely reported. Clinical experience with infants and small children is still very limited and mostly restricted to case reports or small series. Several adult-sized VADs could be implanted in larger adolescent patients, however, they are only suitable for patients with BSA larger than 1.2 m^2 and require

pump flows > 2 L/min. Although clinical outcomes of applying this kind of devices in children with cardiomyopathy or myocarditis is generally good, this is often associated with an increased risk of thromboembolic complications, mainly caused by device mismatch which could lead to blood stasis in the pump, or technical problems with adult-size cannulas not fitting well into the vessels of pediatric patients, or systemic hypertension due to large stroke volumes (101). Reinhartz et al. has presented their experience of 19 children with a mean body weight of 31 kg who were supported with the Thoratec System, and the overall survival rate is only 47%.

Berlin Heart EXCOR and Medos HIA are presently the only long-term VADs designed specifically for all-age pediatric population, from the newborn infant to the adolescent. The Berlin Heart EXCOR VAD is mounted with trileaflet polyurethane valves. It consists of different extracorporeal pneumatically driven polyurethane blood pumps with 10, 25, 30, 50, and 60 ml. The smallest pumps could be applied in neonates and small infants with weight of up to 9 kg. The pumps with volume of 25- and 30-ml are suitable for children of up to 25 kg body weight.

Special cannulas made out of silicon connect the blood pumps to the heart. These cannulas are introduced into to the apex of the left ventricle and the ascending aorta for left ventricular support; and for right ventricular support, they were placed into the right atrium and pulmonary artery. The cannulas of Berlin Heart EXCOR VAD exit the patient body via the upper abdominal wall. The middle portion of the cannula was covered by a Dacron velour, which could stimulate rapid growth of tissue as a biological barrier against ascending infections. The pumps are driven by a pulsatile electropneumatic system. All blood-contacting surfaces (including the valves) are coated with heparin, which could efficiently inhibit thrombosis formation. The in-hospital driving unit (Ikus, Berlin Heart, Germany) operates pumps of any size in either univentricular or biventricular model.

In the present study, approximately 70% of the children with BSA < 1.2 m^2 supported by EXCOR survived during the mechanical assist periods, which was similar to the outcomes of larger adolescents and adults on VAD support (102). Of note, in this analysis, overall mortality during support in small children weighted < 20 kg were reduced to less than 30%, which was significantly better than earlier reports using adult-sized devices. Our study confirmed encouraging outcomes with the application of Berlin Heart EXCOR pediatric ventricular assist system in the pediatric end-stage heart failure population.

Since our first successful application of bridge to transplantation in an 8-year old child in 1990, and the subsequent development of the miniaturized Berlin Heart EXCOR VAD which was designed specifically for small children in 1992, substantial changes have been introduced in the indication for device implantation, anticoagulation therapy, and ICU management, and several important modifications have also been made to the EXCOR system, which taken together led to great advancements in overall survival and support duration, especially for neonates and small infants (103). In the early periods, the results of school age children and larger adolescents were quite encouraging; however, the clinical outcomes in newborns and small infants were less than satisfactory. This has changed tremendously within the past few years, and the first year survival in infants receiving EXCOR support is reaching 70%.

One of the major reasons for the great improvement of survival of VAD recipients is the change from atrial to apical cannulation, which has been proved to significantly reduce the risk of neurological complications. This was first successfully performed in our older children, and with the introduction of the specialized smooth miniaturized apex cannula (Berlin Heart AG, Berlin, Germany) at the end of the 1990s, we further applied this technique in newborns. Since then, we have used this technique whenever possible because of its superior unloading of the ventricle compared to left atrial cannulation, significantly decreasing left ventricular pressure with subsequent reduction of the afterload for the right ventricle. Combined with pharmacological right ventricular support, the LVAD can provide sufficient circulatory support, and therefore eliminated the need for implantation of a BiVAD in most pediatric recipients. As a consequence, within the last two decades, the frequency of BiVAD use in our institute has been largely reduced from 68% to 27.4%.

In our center, the decision to use either univentricular or biventricular assist device were based on the etiology of patient heart failure, the considerations regarding the specific anatomy, and personal physiology of each patient. In children with cardiomyopathy, often both ventricles could be affected. However, the right ventricular function could be improved markedly in a part of these children, shortly after the left ventricular assist device insertion. The assumed mechanism seems to be the decreased afterload in the right ventricle.

In clinical practice, we first stabilize the hemodynamics of the resuscitated or critically hemodynamically compromised child by first installing cardiopulmonary bypass (CPB). This gives us sufficient time for the implantation of a single LVAD. Thereafter, we make the decision

depending on the right ventricular function (transesophageal echocardiography) and the measured hemodynamic data, whether additional right heart support is necessary. Notably, in contrast to previous pediatric VAD reports, the present study demonstrated that biventricular support was associated with significantly higher mortality during support as compared to UniVAD. This finding was consistent with the large multicenter adult reports, and actually it was quite reasonable, since preimplant right ventricular failure has been repeatedly proved to be a major cause of morbidity and mortality in VAD recipients (104-106).

Another reason for the great improvement in clinical outcomes of the pediatric VAD population is the anticoagulation therapy. Detailed information of the anticoagulation regime used in pediatric patients has been previously reported by Stiller et al. (36, 98). The current anticoagulation strategy employed at DHZB is as follows: First, close monitoring by measuring PTT in the early postoperative period, with a target range from 60 to 80s. Second, the coagulation status and the impact of heparin were identified by thromboelastography. We closely monitored Antithrombin III, and substituted if the level falls below 70%. Thereafter, platelet aggregation tests should be performed weekly with target activation of 30%, after children started to receive aspirin and dipyridamol (107). Adolescent patients discharged home with VAD support were given phenprocoumon with a target INR of 3-3.5.

As the pump housing is translucent, thrombi can be detected at an early stage and the pump can be replaced. During the recent years, the pump exchange rate in our center has continuously decreased. The current criteria for pump exchange are any thrombus formation in the left pump or in the left-side cannulae, or thrombi of more than a few millimeters or free-floating thrombi of any size in the right pump and cannulae.

Nevertheless, anticoagulation and its monitoring are still a major problem in the pediatric VAD field (108-110). Despite the application of apical inflow cannulation and the modified anticoagulation protocol, neurological accidents in the present study constituted a significant proportion of adverse events after EXCOR insertion, with 30.1% of the children having either an ischemic or hemorrhagic stroke. Of note, almost all the cerebrovascular events happened in small children aged $\leq$ 10 years (21 of 22), and nearly one quarter of them were fatal (5 of 22). Bleeding requiring reoperation was also not insignificant in our recipients. To mitigate these adverse events, further study might be needed to remodify the current anticoagulant regime, and it would

be more appropriate if set based on different age groups, since the effects of anticoagulant agents in small infants and young children might be different from those in adolescents.

Previously, Blume et al. have conducted a multi-institutional, prospective pediatric VAD study using the Pediatric Heart Transplant Study database, which contains data from 23 pediatric heart transplantation centers in North America (11). In their study, 99 pediatric patients receiving VAD support who were listed for transplantation between January 1993 and December 2003 were included. In this cohort, 77% of the patients were successfully bridged to transplantation, with posttransplantation outcomes comparable to those not requiring VAD. However, most of their included pediatric recipients were larger children, and only 1 child aged less than 5 year received long-term VAD support. Furthermore, almost 1/3 of those patients received short-term VAD support, thus might lead to potential bias to their study.

In the present study, the 30-day and 1-year accurate survival rates in pediatric patients after EXCOR implantation were 80.3%, and 55.5%. In addition, although most of our recipients were infants and small children, the overall 76.9% survival rate of the patients listed for transplantation during circulatory support was favorable, and similar to that of prior pediatric studies based on larger adolescents. Posttransplantation survival for the pediatric recipients implanted with EXCOR was identical to those without VAD support, according to the latest report of the registry of the International Society of Heart and Lung Transplantation (111).

Timing of device implantation and patient selection are two most important aspects for improving outcomes in VAD recipients. Same with any kind of support system, making the decision in favor of earlier EXCOR VAD implantation has generated better results, particularly in small children under one year of age. As previously reported by Potapov et al, in this age group, the majority of children were placed on the system in a state of advanced circulatory failure, characterized by irreversible organ shock sequelae and unresponsiveness of the peripheral circulation to alpha-stimulants, so-called vasoplegia, during the early period. Consequently, no children under one year of age survived longer than 30 days after VAD implantation. However, after the introduction of the policy that VAD should be implanted before shock organ failure sets in or, at the latest, at the very first signs of such organ failure, over three quarters of the infants could finally leave the hospital alive (112-116). Blume's study has also presented similar experience, in which the survival rate of pediatric VAD recipients has

significantly increased in the recent era. These encouraging results emphasize the need to further improve candidate selection (11).

Earlier decision-making for VAD support is also very important for children who failed surgery and could not wean from CPB. In our early experience, the decision of VAD insertion in this patient group was often made after protracted courses in the ICU with repeated cardiopulmonary resuscitation, associated with significantly high long-term mortality in these patients. Now, children received VAD implantation during the initial operation, if their myocardial function could not stay stable after surgery and weaning from CPB is apparently impossible. For pediatric patient suffered from chronic end-stage heart failure, levels of natriuretic peptides together with markers of inflammation are important predictors for the optimal time point of VAD insertion. This has already been shown in the adult VAD study (117).

The current strategy for pediatric VAD usage in our institute was based on the following: rapid deterioration of the circulation; critical peripheral perfusion; metabolic acidosis; cardiac index < 2.0 L/min/m^2; mixed venous saturation < 40%; signs of beginning renal and hepatic failure; patient on respirator with mounting FiO2; massively impaired cardiac function as shown by echocardiography; high or rapidly increasing BNP or N-terminal proBNP level.

Previously, several risk factors for pediatric VAD patients have been reported (11). Nevertheless, the included patients in these studies were mainly larger adolescents implanted with adult-sized devices, and the patient number receiving long-term VAD support was relatively small, which might limit the generalizability of their results to the pediatric population. More importantly, these studies included a limited analysis of patient characteristics; therefore, many potentially important preoperative risk assessment parameters might have been missed. As the increased use of ventricular assist device support in pediatric patients with advanced heart failure, risk factors and clinical indications for VAD implantation in this population need to be clarified.

We conducted this retrospective study in order to better identify predictors for post-VAD survival in children, with the hope of improving pediatric VAD candidate selection. Preoperative characteristics associated with increased risk of in-hospital death were the congenital etiology and CVP > 17 mmHg. Further analysis demonstrated that the high-risk patient group was associated with significantly elevated mortality as compared to those recipients without any risk factor.

Reports from the International Society for Heart and Lung Transplantation and other multicenter studies have demonstrated significantly worse outcomes in children with congenital heart disease undergoing heart transplantation compared with other pediatric recipients (118-119). Similarly, in this study, the presence of congenital disease was associated with the highest negative impact on survival in children after VAD implantation, with a 67% in hospital mortality in children with congenital heart disease compared to 23% in those with a non-congenital etiology. Others have found similarly poorer outcomes in CHD patients undergoing VAD support. There might be several reasons for the reduced survival in this patient group. CHD children often have hypoxia and right heart failure, as well as secondary liver and renal dysfunction. Therefore, the preoperative physiological state of CHD patients is likely considerably worse than that of the noncongenital population. In addition, children with CHD are more likely to have received repeated surgical interventions to repair cardiac anomalies prior to VAD implantation, which increase the operative complexity encourntered on repeat sternotomy.

Elevated central venous pressure may reflect the worsening right ventricular function in patients with cardiovascular disease, and has been reported to be predictive of the development of right ventricular failure after VAD implantation. Right heart failure in adults and children is associated with high post-VAD morbidity and mortality, likely due to the impact of a dysfunctional right ventricle on hepatic and renal function and, therefore, overall operative risk. In this analysis, pediatric patients with an elevated CVP had significantly higher odds of death. Corroborating our finding, a cohort study of adult VAD recipients by Rao et al. also identified increased CVP as an independent predictor for post-VAD mortality (120-121).

Additionally, it was worthwhile to note that age-dependent factors (such as age, BSA, body mass index, et al.) were not correlated with different patient survival outcomes after implantation, even in our initial univariate analysis, which supported our point that EXCOR could provide satisfactory support and had comparable clinical outcomes in both small children and larger adolescent patients.

The present study has several limitations that merit attention. First, this was a single-center, retrospective cohort study and is therefore subject to inherent bias and confounding. Additionally, the relatively small patient sample limits study power. Thus, unadjusted p-values provided for univariable analysis should be interpreted in the context of risk for a type I error. However, we

feel that Bonferroni p value adjustment in this exploratory analysis may lead to a dismissal of clinically relevant data. Furthermore, in pediatric studies of long-term mechanical circulatory support, power limitations are inherently hard to avoid due to the current low device utilization rates. Finally, the present study included both children supported with LVAD and BiVAD, which might cause bias to our analysis. However, the strategy in our center for BiVAD implantation is to firstly implant a LVAD combined with pharmacological right ventricular support, and then decide if there is a need for an additional right ventricular assist device, according to the performance of right ventricular function; thus, most of our children received LVAD implantation primarily. Additionally, our study also showed that the type of VAD support did not affect the risk factor analysis.

6. Zusammenfassung

Hintergrund: Um das versagende Herz von Babys und Kleinkindern zu unterstützen, werden bei Pädiatriepatienten mit Herzerkrankungen im Endstadium routinemäßig verschiedene Geräte angewandt, was eine Zwischenlösung bis zur Transplantation oder Myokarderholung darstellt. Obwohl extrakorporale Membranoxygenierung (ECMO) und Zentrifugenpumpen seit der Entwicklung der Chirurgie am Kinderherzen häufig und erfolgreich eingesetzt werdern, ist ihr Einsatz doch stark durch ihre nur kurzwährende Unterstützung und die Immobilisation des Patienten eingeschränkt. Verschiedene Herzunterstützungssysteme (Ventricular assist device, VAD) für Erwachsene könnten in größere Jugendliche implantiert werden, aber sie können keine Kreislaufunterstützung bei kleineren Kindern unter 20 Kilogramm bieten. Derzeit sind die Erfahrungen von dem Einsatz von VADs in Kindern begrenzt, und bisherige Studien beziehen sich hauptsächlich entweder auf VADs für Erwachsene oder auf eine recht kleine Patientenzahl. Wir beschreiben unsere Erfahrungen mit mechanischer Langzeit-Kreislaufunterstützung bei Kindern und jungen Heranwachsenden mit beständigem Herzversagen über die letzten zehn Jahre. Dabei verwandten wir Berlin Heart EXCOR VAD (Berlin Heart AG, Berlin, Germany) das speziell für alle Alter und Gruppen pediatrische Patienten entwickelt wurde. Ausserdem erläutern wir potentielle Risikofaktoren für postimplantative Sterblichkeit von Kindern.

Methoden: Zwischen Januar 1999 und Dezember 2009 wurde 73 Kindern am Deutschen Herzzentrum Berlin das Berlin Heart EXCOR VAD implantiert. Wir betrieben eine retrospektive, nicht-zufällige Studie anhand von Patientendaten von der VAD-Registratur der Datenbank des Deutschen Herzzentrums Berlin. Folgende klinische Daten wurden gesammelt und analysiert. (1) Patientenkenndaten: Alter, Geschlecht, Körperoberfläche, Körperlänge, Gewicht, Body Mass Index, Körpertemperatur, Sauerstoffsättigung, Ursache für das Herzversagen, zuvorige Sternotomie, Krankengeschichte von Nebenerkrankungen, VAD-Typ, Jahr der Implantierung; (2) medizinische und apparative Behandlung des Herzversagens: Präimplantative Herz-Lungenreanimation, intravenöse Inotrope, Vasopressoren, Vasodilatoren, Diuretika, antiarrhythmische Therapie, andere mechanische Kreislaufunterstützung vor EXCOR Implantierung; (3) Hämodynamische Messung des Schweregrades des Herzversagens: Linksventrikuläre Ejektionsfraktion, Blutdruck (systolisch, diastolisch, mittlerer), Herzfrequenz, Rhythmus, Sauerstoffsättigung, zentralvenöser Druck, pulmonalarterieller Druck (systolisch, diastolisch, mittlerer), pulmonalkapillärer Druck, Herzauswurfvolumen und Index; (4)

Labordaten (< 24 Stunden vor VAD Implantation): Serum Natrium-, Kalzium- und Glukosekonzentration, Hämoglobin, Leukozytenzählung, Hämatokrit, Plättchenzählung, INR, partielle Thromboplastinzeit, Aktivität von Alanin- und Aspartat-Aminotransferase, Laktatdehydrogenase, Kreatinkinase-MB, γ-Glutanyltranspeptidase, Gesamtbilirubinkonzentration, Albuminkonzentration, Gesamtprotein, Harnstoff-Stickstoff im Blut, Serum Kreatininkonzentration, Serum C-reaktives Protein; (5) klinische Erfolge: Beatmungsdauer, Dauer der intensivmedizinischen Behandlung, Dauer der Unterstützung durch EXCOR, Gründe für die Entnahme des EXCOR, Todesursache, posttransplantäres Überleben und ungünstige Vorfälle.

Ergebnisse: Die Ethiologie des Myokardversagens im Endstadium umfasste kongenitale (72%) und erworbene Herzerkrankungen (27%); das mittlere Alter zum Zeitpunkt der Implantation betrug vier Jahre (12 Tage bis 17 Jahre) und die mittlere Unterstützungszeit betrug 59 Tage (1 bis 432 Tage). Bei 33 Patienten wurde der Zeitraum bis zu einer Herztransplantation überbrückt, bei 14 Patienten wurde das Gerät nach myokardialer Erholung entnommen, zwei wurden fortbestehend mit dem VAD behandelt und die übrigen 24 Patienten verstarben während der Behandlung. Die genaue Überlebensrate 30 Tagen, bzw ein Jahr nach dem Einsetzen des EXCOR betrug 80,3%, bzw 55,5%. Von den 56 Kindern aus der Gruppe, die auf der Transplantationsliste stehen, konnten 77% die Unterstützungszeit überleben. Zwischen kleinen Kindern mit BSA < 1.2 m2 und größeren Heranwachsenden wurden keine unterschiedlichen klinischen Folgen festgestellt, mit Ausnahme eines höheren Vorkommens von Schlaganfällen bei den kleinen Patienten. Patienten mit einem BiVAD zeigten eine signifikant höhere postimplantative Sterblichkeit gegenüber Kindern mit UniVAD. Eine geringere postimplantäre Überlebensrate wurde auch bei Patienten mit einer kongenitalen Herzerkrankung gegenüber einer nicht ererbten Diagnose beobachtet. Unsere multivariate Statistik macht deutlich, dass eine erbliche Diagnose und ein zentralvenöser Druck über 17 mmHg eigenständige Risikofaktoren für das Überleben einer EXCOR-Implantation sind. Bei Patienten ohne einen dieser Faktoren ergab sich eine Überlebensrate nach 30 Tagen bzw einem Jahr von 92,2%±4,4% bzw 75,9%±8,3%; bei der kombinierten Gruppe mit wenigstens einem Risikofaktor ergaben 75,9%±8,3% bzw 29,7%±10,4%.

Fazit: (1) Das Berlin Heart EXCOR VAD leistet eine effiziente und verlässliche Kreislaufunterstützung sowohl bei Kleinkindern, als auch bei größeren Heranwachsenden mit einer Herzerkrankung im Endstadium, mit viel versprechenden klinischen Ergebnissen

vergleichbar mit denen erwachsener VAD-Patienten. (2) Empfänger eines UniVAD zeigten eine signifikant höhere Überlebensrate im Vergleich der Empfänger eines BiVAD. Die Gesamtüberlebensrate bis zur Transplantation, Regeneration der Ventrikelfunktion oder fortwährender apparativer Unterstützung war bei Patienten mit einer angeborenen Herzerkrankung signifikant geringer als bei Kindern mit einer erworbenen Diagnose; (3) Das Vorkommen von bestimmten Komplikationen (wie Cerebrovasculärer Unfall) bleibt bei diesen Beobachtungen hoch, besonders bei kleinen pädiatrischen Patienten, was den Bedarf einer weiteren Verbesserung der Antikoagulationstherapie bei Kindern nach einer VAD-Verpflanzung nahe legt; (4) Das Vorhandensein einer kongenitalen Herzerkrankung und eines zentralvenösen Druckes von übe 17 mmHg waren unabhängige Risikofaktoren für die postimplantative Überlebensrate von Kindern mit einem EXCOR VAD. Weitere Auswertungen verdeutlichten, dass die Gruppe der Risikopatienten mit einer signifikant höheren Mortalitätsrate verbunden war als die Patientengruppe ohne Risikofaktor. Interessanterweise waren altersbedingte Faktoren nicht mit unterschiedlichen Überlebensraten nach der Implantation korreliert, genauso wie auch bei unserer früheren Analyse, die unsere Vermutung bestätigte, dass das EXCOR eine zufriedenstellende Unterstützung leistet und vergleichbare klinische Ergebnisse sowohl bei Kleinkindern, als auch bei jugendlichen Patienten.

7. Summary

Background: To assist the failing heart in infants and small children, mechanical circulatory support with a variety of devices has been routinely applied in pediatric patients with end-stage heart disease, aiming at bridge to transplantation or myocardial recovery. Although extracorporeal membrane oxygenation (ECMO) and centrifugal pumps have been widely and successfully used since the development of pediatric cardiac surgery, their applications are largely limited by the short-term support and immobilization of the patient. Several adult-sized ventricular assist devices (VADs) could be implanted in larger adolescent patients, but they could not provide circulatory support in small children with weight less than 20 kg. Current experience with the use of pediatric-specific VADs in children is limited, and previous studies were mostly based on either adult-sized VADs or relatively small patient numbers. We describe our recent 10-year experience with long-term mechanical circulatory support in small children and young adolescents with intractable heart failure, using Berlin Heart EXCOR Pediatric VAD (Berlin Heart AG, Berlin, Germany), which is designed specifically for all age groups of the pediatric population, and further define the potential risk factors for postimplantation mortality in children.

Methods: Between 01/1999 Jan and 12/2009 Dec, 73 children were implanted with the Berlin Heart EXCOR pediatric ventricular assist device at the Deutsches Herzzentrum Berlin. We conducted a retrospective, non-randomized study by obtaining patient data from the ventricular assist device registry database of our institution. The following clinical data were collected and analyzed: (1) patient characteristics: age, sex, body surface area, body length, weight, body mass index, temperature, pulse oxygen saturation, causes of heart failure, prior sternotomy, history of comorbidities, VAD type, year of implantation; (2) medical and device therapy for heart failure: preimplantation cardiac pulmonary resuscitation, intravenous inotropes, vasopressor, vasodilators, diuretics, antiarrhythmic therapy, other mechanical circulatory support before EXCOR implantation; (3) measures of hemodynamic severity of heart failure: LVEF, blood pressure (systolic, diastolic, mean), heart rate, rhythm, pulse oxygen saturation, central venous pressure, pulmonary artery pressure (systolic, diastolic, mean), pulmonary capillary wedge pressure, cardiac output and index; (4) laboratory data (< 24 hours before VAD implantation): serum sodium concentration, serum potassium concentration, serum glucose concentration, hemoglobin, white blood count, hematocrit, platelet count, international normalization ratio, partial thromboplastin time, alanine and aspartate aminotransferase activity, lactate

dehydrogenase, creatine kinase-MB, γ-glutamyl transpeptadase, total bilirubin concentration, albumin concentration, total protein, blood urea nitrogen, serum creatinine concentration, serum C-reactive protein; (5) clinical outcomes: duration of ventilation, period of ICU stay, duration of EXCOR support, causes of EXCOR explantation, cause of death, posttransplantation survival, and adverse events.

Results: The etiology of end-stage myocardial failure included non-congenital (72%) and congenital heart disease (27%); the median age at implantation was 4 years (12 days to 17 years), and the median support time was 59 days (1 to 432 days). Thirty-three patients were bridged to heart transplantation, 14 were explanted following myocardial recovery, 2 continued to receive support, and the other 24 died on support. The accurate rate of survival at 30 days and 1 year after EXCOR implantation was 80.3% and 55.5%, respectively. For the subset of 56 children listed for transplantation, 77% survived during the support period. No differences in clinical outcomes between small children with BSA < 1.2 m^2 and larger children were observed, except that there was a higher incidence of stroke in small recipients. Patients supported with a biventricular assist device had significantly higher postimplantation mortality as compared to children with UniVAD. Lower postimplantation survival was also observed in patients with congenital cardiac disease compared with children with a non-congenital diagnosis. Our multivariate analysis revealed that congenital diagnosis and CVP > 17 mmHg were independent risk factors for survival after EXCOR implantation. For patients without any of these factors, the 30-day and 1-year survival after EXCOR implantation was 92.2%±4.4% and 75.9%±8.3%; for the combined group with at least 1 risk factor, it was 75.9%±8.3% and 29.7%±10.4%, respectively.

Conclusions: (1) The Berlin Heart EXCOR pediatric VAD provides efficient and reliable mechanical circulatory support in both small children and larger adolescents suffered from end-stage heart disease, with encouraging clinical outcomes comparable to those in adult VAD patients; (2) UniVAD recipients had significantly better survival, as compared with patients supported with BiVAD. The overall survival to transplantation, recovery of ventricular function, or ongoing device support for patients with congenital heart disease were also significantly lower than in children with a non-congenital diagnosis; (3) Incidences of certain complications (such as cerebralvascular accident) in our study remained high (especially in small pediatric patients), which might emphasize the need of further improvement in anticoagulation therapy for children

after VAD implantation; (4) The presence of congenital heart disease and CVP > 17 mmHg were independent risk factors for postimplantation survival of children supported with EXCOR VAD. Further analysis demonstrated that the high-risk patient group was associated with significantly elevated mortality as compared to those recipients without any risk factor. (5) Of note, age-dependent factors were not correlated with different patient survival outcomes after implantation, even in our initial univariate analysis, which supported our point that EXCOR can provide satisfactory support and has comparable clinical outcomes in both small children and larger adolescent patients.

8. References

1. Christianson A, Howson CP, Modell B. March of Dimes Global Report on Birth Defects: The Hidden Toll of Dying and Disabled Children. White Plains, NY, March of Dimes Birth Defects Foundation, 2006.
2. Ashburn DA, McCrindle BW, Tchervenkov CI, et al. Outcomes after the Norwood operation in neonates with critical aortic valve stenosis or aortic valve atresia. J Thorac Cardiovasc Surg 2003; 125: 1070-1082.
3. Rosenthal D, Bernstein D: Pediatric mechanical circulatory support: Challenges and opportunities. Circulation 2006; 113: 2266-2268.
4. Boucek MM, Edwards LB, Keck BM, et al. Registry of the international society for heart and lung transplantation: Eighth official pediatric report-2005. J Heart Lung Transplant 2005; 24: 968-982.
5. Fogel MA, Durning S, Wernovsky G, et al. Brain versus lung: Hierarchy of feedback loops in single-ventricle patients with superior cavopulmonary connection. Circulation 2004; 110(11 suppl 1): II-147–II-152.
6. Khambadkone S, Li J, de Leval MR, et al. Basal pulmonary vascular resistance and nitric oxide responsiveness late after Fontan type operation. Circulation 2003; 107: 3204-3208.
7. Arola A, Jokinen E, Ruuskanen O, et al. Epidemiology of idiopathic cardiomyopathies in children and adolescents: A nationwide study in Finland. Am J Epidemiol 1997; 146: 1-9.
8. Arola A, Tuominen J, Ruuskanen O, et al. Idiopathic dilated cardiomyopathy in children: Prognostic indicators and outcome. Pediatrics 1997; 101: 369-376.
9. Chang A, McKenzie ED. Mechanical cardiopulmonary support in children and young adults: Extracorporeal membrane oxygenation, ventricular assist devices, and long-term support devices. Pediatr Cardiol 2005; 26: 2-28.
10. Kocher AA, Schlechta B, Ehrlich M, et al. Outcome of pediatric heart transplantation: An analysis of 27 cases. Transplant Proceeding 2001; 33: 2834-2835.
11. Blume ED, Naftel DC, Bastardi HJ, et al; Pediatric Heart Transplant Study Investigators. Outcomes of children bridged to heart transplantation with ventricular assist devices: A multi-institutional study. Circulation 2006; 113: 2313-2319.
12. Throckmorton AL, Allaire PE, Gutgesell HP et al. Pediatric circulatory support systems. ASAIO J 2002; 48: 216-221.
13. Throckmorton AL, Untaroiu A. CFD analysis of a Mag-Lev ventricular assist device for

infants and children: Fourth generation design. ASAIO J 2008; 54: 423-431.
14. Throckmorton AL, Untaroiu A, Allaire PE, et al. Numerical design and experimental hydraulic testing of an axial flow VAD for infants and children. ASAIO J 2007; 53: 754-761.
15. Baldwin JT, Borovetz HS, Duncan BW, et al. The National, Heart, Lung, and Blood Institute Pediatric Circulatory Support Program. Circulation 2006; 113: 147-155.
16. Weiss W. Pulsatile pediatric ventricular assist devices. ASAIO J 2005; 51: 540-545.
17. Fynn-Thompson AC. Pediatric ventricular assist devices. Pediatric Cardiology 2007; 28: 149-155.
18. Thuys C, Mullaly R, Horton S. Centrifugal ventricular assist in children under 6 kg. Eur J Cardiotriorac Surg 1998; 13:130-134.
19. Reinhartz O, Hill D, Al-Khaldi A, et al. Thoratec ventricular assist devices in pediatric patients: update on clinical results. ASAIO J 2005; 51:501-503.
20. Sadeghi AM, Marelli D, Talamo M, et al. Short-term bridge to transplant using the BVS 5000 in a 22-kg child. Ann Thorac Surg 2000; 70: 2151-2153.
21. ECLS Registry Report. Extracorporeal Life Support Organization, 2006.
22. Duncan BW. Mechanical circulatory support for infants and children with cardiac disease. Ann Thorac Surg 2002; 73: 1670-1677.
23. Duncan BW. Pediatric mechanical circulatory support. ASAIO J 2005; 51: ix–xiv.
24. Duncan BW, Hraska V, Jonas RA, et al. Mechanical circulatory support in children with cardiac disease. J Thorac Cardiovasc Surg 1999; 117: 529-542.
25. Duncan BW, Ibrahim AE, Hraska V, et al. Use of rapid-deployment extracorporeal membrane oxygenation for the resuscitation of pediatric patients with heart disease after cardiac arrest. J Thorac Cardiovasc Surg 1998; 116: 305-311.
26. Agati S, Ciccarello G, Ocello S, et al. Pulsatile ECMO and VAD: a dual use of a new device in pediatric cardiac patients. ASAIO J 2006; 52: 501-504.
27. Hannan RL, Ojito JW, Ybarra MA, et al. Rapid cardiopulmonary support in children with heart disease: a nine-year experience. Ann Thorac Surg 2006; 82: 1637-1641.
28. Ravishankar C, Dominguez TE, Kreutzer J, et al. Extracorporeal membrane oxygenation after stage I reconstruction for hypoplastic left heart syndrome. Pediatr Crit Care Med 2006; 7: 319-323.
29. MorrisMC, Wernovsky G, Nadkarni VM. Survival outcomes after extracorporeal cardiopulmonary resuscitation instituted during active chest compressions following refractory in-hospital pediatric cardiac arrest. Pediatr Crit Care Med 2004; 5: 440-446.
30. Duncan BW. Matching the mechanical circulatory support device to the child with heart

failure. ASAIO J 2006; 52: e15-e21.

31. Allan CK, Thiagarajan RR, del Nido PJ, et al. Indication for initiation of mechanical circulatory support impacts survival of infants with shunted single-ventricle circulation supported with extracorporeal membrane oxygenation. J Thorac Cardiovasc Surg 2007; 133: 660-667.
32. Karl TR. Circulatory support in children. In Mechanical Circulatory Support 1997, 7-20.
33. Karl TR, Sano S, Horton S, et al. Centrifugal pump left heart assist in pediatric cardiac operations. Indication, technique, and results. J Thorac Cardiovasc Surg 1991; 102: 624-630.
34. del Nido PJ, Duncan BW, Mayer JE Jr, et al. Left ventricular assist device improves survival in children with left ventricular dysfunction after repair of anomalous origin of the left coronary artery from the pulmonary artery. Ann Thorac Surg 1999; 67: 169-172.
35. Karl TR, Horton SB, Brizard C. Postoperative support with the centrifugal pump ventricular assist device (VAD). Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann 2006; 9: 83-91.
36. Stiller B, Weng Y, Hübler M, et al. Pneumatic pulsatile ventricular assist devices in children under 1 year of age. Eur J Cardiothorac Surg 2005; 28: 234-239.
37. Reinhartz O, Stiller B, Eilers R, et al. Current clinical status of pulsatile pediatric circulatory support. ASAIO J 2002; 48: 455-459.
38. Stiller B, Lange PE, Hetzer R, et al. Left ventricular assist device. N Engl J Med 2002; 13: 1023.
39. Hetzer R, Loebe M, Potapov EV, et al. Circulatory support with pneumatic paracorporeal ventricular assist device in infants and children. Ann Thorac Surg 1998; 66: 1498-1506.
40. Kaczmarek I, Mair H, Groetzner J, et al. Mechanical circulatory support in infants and adults with the MEDOS/HIA assist device. Artif Organs 2005; 29: 857-860.
41. Konertz WF. Clinical applications in children of the Medos ventricular assist device. In Mechanical support for cardiac and respiratory failure in pediatric patients 2001, 269-285 (Ed. Duncan BW) New York: Marcel Dekker.
42. Konertz W, Hotz H, Schneider M, et al. Clinical experience with the MEDOS HIA-VAD system in infants and children: a preliminary report. Ann Thorac Surg 1997; 63: 1138-1144.
43. Ishino K, Loebe M, Uhlemann F, et al. Circulatory support with paracorporeal pneumatic ventricular assist device (VAD) in infants and children. Eur J Cardiothorac Surg 1997; 11: 965-972.
44. Stiller B, Hetzer R, Weng Y, et al. Heart transplantation in children after mechanical circulatory support with pulsatile pneumatic assist device. J Heart Lung Transplant 2003; 22: 1201-1208.

45. Merkle F, Boettcher W, Stiller B, et al. Pulsatile mechanical cardiac assistance in pediatric patients with the Berlin heart ventricular assist device. J Extra Corpor Technol 2003; 35: 115-120.
46. Reinhartz O, Keith FM, El-Banayosy A, et al. Multicenter experience with the Thoratec ventricular assist device in children and adolescents. J Heart Lung Transplant 2001; 20: 439-448.
47. Takano H, Nakatani T. Ventricular assist systems: experience in Japan with Toyobo pump and Zeon pump. Ann Thorac Surg 1996; 61: 317–322.
48. Ashton RC, Oz MC, Michler RE, et al. Left ventricular assist device options in pediatric patients. ASAIO J 1995; 41: M277-M280.
49. Daily BB, Pettitt TW, Sutera SP, et al. Pierce-Donachy pediatric VAD: progress in development. Ann Thorac Surg 1996; 61: 437-443.
50. Hetzer R, Weng Y, Potapov EV, et al. First experiences with a novel magnetically suspended axial flow left ventricular assist device. Eur J Cardiothorac Surg 2004; 25: 964-970.
51. Song X, Throckmorton AL, Untaroiu A, et al. Axial flow blood pumps. ASAIO J 2003; 49: 355-364.
52. Potapov EV, Nasseri BA, Loebe M, et al. Transcranial detection of microembolic signals in patients with a novel nonpulsatile implantable LVAD. ASAIO J 2001; 47: 249-253.
53. Morales DL, Dibardino DJ, McKenzie ED, et al. Lessons learned from the first application of the DeBakey VAD Child: an intracorporeal ventricular assist device for children. Heart Lung Transplant 2005; 24: 331-337.
54. Merkle F, Boettcher W, Stiller B, et al. Pulsatile mechanical cardiac assistance in pediatric patients with the Berlin heart ventricular assist device.J Extra Corpor Technol 2003; 35: 115-120.
55. Kaufmann F, Hennig E, Loebe M, et al. Improving the antithrombogenity of artificial surfaces through heparin coating-clinical experience with the pneumatic extracorporeal Berlin heart assist device. J für Anästhesie und Intensivbehandlung 1997; 4: 56-60.
56. Koster A, Loebe M, Sodian R, et al. Heparin antibodies and thromboembolism in heparin-coated and noncoated ventricular assist devices. J Thorac Cardiovasc Surg 2001;121:331-335.
57. Riesenfeld J, Olsson P, Sanchez J, et al. Surface modification with functionally active heparin. Heparin antibodies and thromboembolism in heparin-coated and noncoated ventricular assist devices. Med Device Technol 1995; 6: 24-31
58. Ghez O, Liesner R, Karimova A, et al. Subcutaneous low molecular weight heparin for

management of anticoagulation in infants on Excor ventricular assist device. ASAIO J 2006; 52(6): 705-707.

59. Potapov EV, Ignatenko S, Nasseri BA, et al. Clinical significance of PlA polymorphism of platelet GP IIb/IIIa receptors during long-term VAD support. Ann Thorac Surg 2004; 77(3): 869-874.
60. Koster A, Huebler S, Potapov E, et al. Impact of heparin-induced thrombocytopenia on outcome in patients with ventricular assist device support: single-institution experience in 358 consecutive patients. Ann Thorac Surg 2007; 83(1): 72-76.
61. Hetzer R, Potapov E, Stiller B, et al. Improvement in survival after mechanical circulatory support with pneumatic pulsatile ventricular assist devices in pediatric patients. Ann Thorac Surg 2006; 82: 917-924.
62. Stiller B, Dahnert I, Weng YG, et al. Children may survive severe myocarditis with prolonged use of biventricular assist devices. Heart 1999; 82: 237-240.
63. Drews TN, Loebe M, Jurmann MJ, et al. Outpatients on mechanical circulatory support. Ann Thorac Surg. 2003; 75(3): 780-785.
64. Ibrahim AE, Duncan BW, Blume ED, et al. Long-term follow-up of pediatric cardiac patients requiring mechanical circulatory support. Ann Thorac Surg. 2000; 69: 186-192.
65. Del Nido PJ, Armitage JM, Ficker FJ, et al. Extracorporeal membrane oxygenation support as a bridge to pediatric heart transplantation. Circulation 1994; 90(pt 2): II-66–II-69.
66. Fiser WP, Yetman AT, Gunselman RJ, et al. Pediatric arteriovenous extracorporeal membrane oxygenation (ECMO) as a bridge to cardiac transplantation. J Heart Lung Transplant 2003; 22: 770 –777.
67. Imamura M, Hale S, Johnson CE, et al. The first successful DeBakey VAD child implantation as a bridge to transplant. ASAIO J 2005; 51: 670 –672.
68. Imamura M, Dossey AM, Prodhan P, et al. Bridge to cardiac transplant in children: Berlin Heart versus extracorporeal membrane oxygenation. Ann Thorac Surg. 2009; 87(6): 1894-1901.
69. Sharma MS, Webber SA, Morell VO, et al. Ventricular assist device support in children and adolescents as a bridge to heart transplantation/ Ann Thorac Surg 2006; 82(3): 926-932.
70. Gilmore H, Millar KJ, Weintraub RG, et al. Australian experience with VAD as a bridge to paediatric cardiac transplantation. Heart Lung Circ 2010; 19(1): 26-30.
71. Januszewska K, Malec E, Birnbaum J, et al. Ventricular assist device as a bridge to heart transplantation in children. Interact Cardiovasc Thorac Surg 2009; (5): 807-810.
72. Rockett SR, Bryant JC, Morrow WR, et al. Preliminary single center North American

experience with the Berlin Heart pediatric EXCOR device. ASAIO J 2008; 54(5): 479-482.

73. Husain SA, Wallis G, Fricker FJ, et al. Ventricular assist device implantation in the pediatric population: does pump size selection and associated hemodynamics impact outcomes? ASAIO J. 2008; 54(5): 474-478.
74. O'Connor MJ, Menteer J, Chrisant MR, et al. Ventricular assist device-associated anti-human leukocyte antigen antibody sensitization in pediatric patients bridged to heart transplantation. J Heart Lung Transplant 2010; 29(1): 109-116.
75. Reddy SL, Hasan A, Hamilton LR, et al. Mechanical versus medical bridge to transplantation in children. What is the best timing for mechanical bridge? Eur J Cardiothorac Surg 2004; 25(4): 605-609.
76. Mohapatra B, Vick GW 3rd, Fraser CD Jr, et al. Short-term mechanical unloading and reverse remodeling of failing hearts in children. J Heart Lung Transplant. 2010; 29(1): 98-104.
77. Cassidy J, Haynes S, Kirk R, et al. Changing patterns of bridging to heart transplantation in children. J Heart Lung Transplant. 2009; 28(3): 249-254.
78. Hill JD, Reinhartz O. Clinical outcomes in pediatric patients implanted with Thoratec ventricular assist device. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2006: 115-122.
79. Gandhi SK, Huddleston CB, Balzer DT, et al. Biventricular assist devices as a bridge to heart transplantation in small children. Circulation. 2008; 118(14 Suppl): S89-S93.
80. Boucek MM, Novick RJ, Bennett LE, et al. The Registry of the International Society for Heart and Lung Transplantation: second official pediatric report-1998. J Heart Lung Transplant 1998; 17: 1141-1160.
81. Morrow WR, Naftel D, Chinnock R, et al. Outcome of listing for heart transplantation in infants younger than six months: predictors of death and interval to transplantation. The Pediatric Heart Transplantation Study Group. J Heart Lung Transplant 1997; 16: 1255-1266.
82. Mehta U, Laks H, Sadeghi A, et al. Extracorporeal membrane oxygenation for cardiac support in pediatric patients. Am Surg 2000; 66: 879-886.
83. Pennington DG, Swartz MT. Circulatory support in infants and children. Ann Thorac Surg 1993; 55: 233-237.
84. Aharon AS, Drinkwater DC Jr, Churchwell KB, et al. Extracorporeal membrane oxygenation in children after repair of congenital cardiac lesions. Ann Thorac Surg 2001: 72: 2095-2101.
85. Bartlett RH, Gazzaniga AB, Jefferies MR, et al. Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infancy. Trans Am Soc Artif Intern Organs 1976; 22:

80-93.

86. Conrad SA, Rycus PT, Dalton H. Extracorporeal life support registry report 2004. ASAIO J 2005: 51: 4-10.
87. Ishino K, Weng Y, Alexi-Meskishvili V, et al. Extracorporeal membrane oxygenation as a bridge to cardiac transplantation in children. Artif Organs 1996: 20: 728-732.
88. Frazier OH, Bricker JT, Macris MP, et al. Use of a left ventricular assist device as a bridge to transplantation in a pediatric patient. Tex Heart Inst J 1989; 16: 46-50.
89. Matsuda H, Matsuwaka R, Kaneko M, et al. Analysis of clinical factors for survival after left and biventricular bypass using centrifugal pump following open heart surgery in infants and adults. Artif Organs 1990: 14: 382-386.
90. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. N Engl J Med 2001;345: 1435-1443.
91. Hetzer R, Muller J, Weng Y, et al. Cardiac recovery in dilated cardiomyopathy by unloading with a left ventricular assist device. Ann Thorac Surg 1999; 68: 742-749.
92. Hetzer R, Hennig E, Schiessler A, et al. Mechanical circulatory support and heart transplantation. J Heart Lung Transplant 1992; 11: S175-S181.
93. Deng MC, Edwards LB, Hertz MI, et al. Mechanical circulatory support device database of the International Society for Heart and Lung Transplantation: Third Annual Report - 2005. J Heart Lung Transplant 2005; 24: 1182-1187.
94. Potapov EV, Jurmann MJ, Drews T, et al. Patients supported for over 4 years with left ventricular assist devices. Eur J Heart Fail 2006; 8(7): 756-759.
95. Dandel M, Weng Y, Siniawski H, et al. Long-term results in patients with idiopathic dilated cardiomyopathy after weaning from left ventricular assist devices. Circulation 2005; 112(Suppl.): I37-I45.
96. Hendry PJ, Masters RG, Davies RA, et al. Mechanical circulatory support for adolescent patients: The Ottawa Heart Institute experience. Can J Cardiol 2003; 19: 409-412.
97. Hetzer R, Loebe M, Alexi-Meskishvili V, et al. Pulsatile pediatric assist devices: Current results for bridge to transplantation. Semin Thorac Cardiovasc Surg. Pediatr Card Surg Annu 1999: 157-175.
98. Stiller B, Lemmer J, Merkle F, et al. Consumption of blood products during mechanical circulatory support in children: Comparison between ECMO and a pulsatile ventricular assist device. Intensive Care Med 2004: 30: 1814-1820.
99. McKenna Jr DH, Eastlund T, Segall M, et al. HLA alloimmunization in patients requiring ventricular assist device support. J Heart Lung Transplant 2002: 21: 1218-1224.

100. Warnecke H, Berdjis F, Hennig E, et al. Mechanical left ventricular support as a bridge to cardiac transplantation in childhood. Eur J Cardiothorac Surg 1991; 5: 330-333.
101. Reinhartz O, Copeland JG, Farrar DJ. Thoratec ventricular assist devices in children with less than 1.3 m2 of body surface area. Am Soc Artif Intern Organs J 2003; 49: 727-730.
102. Kirklin JK, Naftel DC, Kormos RL, et al. Second INTERMACS annual report: more than 1,000 primary left ventricular assist device implants. J Heart Lung Transplant 2010; 29(1): 1-10.
103. Hetzer R, Stiller B. Technology insight: Use of ventricular assist devices in children. Nat Clin Pract Cardiovasc Med 2006: 3: 377-386.
104. Ochiai Y, McCarthy PM, Smedira NG, et al. Predictors of severe right ventricular failure after implantable left ventricular assist device insertion: analysis of 245 patients.Circulation 24; 106(12 Suppl 1): I198-I202.
105. Drakos SG, Janicki L, Horne BD, et al. Risk factors predictive of right ventricular failure after left ventricular assist device implantation. Am J Cardiol. 2010 Apr 1;105(7):1030-1035.
106. Matthews JC, Koelling TM, Pagani FD, et al. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. J Am Coll Cardiol. 2008; 51(22): 2163-2172.
107. Potapov EV, Ignatenko S, Nasseri BA, et al. Clinical significance of PlA polymorphism of platelet GP IIb/IIIa receptors during long-term VAD support. Ann Thorac Surg 2004; 77: 869-874.
108. Takahama T, Kanai F, Onishi K. Anticoagulation during use of a left ventricular assist device. ASAIO J 2000; 46: 354-357.
109. Spanier T, Oz M, Levin H, et al. Activation of coagulation and fibrinolytic pathways in patients with left ventricular assist devices. J Thorac Cardiovasc Surg 1996; 112: 1090-1097.
110. Schmid C, Weyand M, Hammel D, et al. Effect of platelet inhibitors on thromboembolism after implantation of a Novacor N100 - Preliminary results. Thorac Cardiovasc Surg 1998; 46: 260-262.
111. Kirk R, Edwards LB, Aurora P, et al. Registry of the International Society for Heart and Lung Transplantation: Twelfth Official Pediatric Heart Transplantation Report-2009. J Heart Lung Transplant. 2009; 28(10): 993-1006.
112. Deng MC, Weyand M, Hammel D, et al. Selection and management of ventricular assist device patients: The Muenster experience. J Heart Lung Transplant 2000; 19(Suppl.): S77-S82.
113. Deng MC, Loebe M, El-Banayosy A, et al. Mechanical circulatory support for advanced heart

failure: Effect of patient selection on outcome. Circulation 2001; 103: 231-237.

114. El-Banayosy A, Arusoglu L, Kizner L, et al. Predictors of survival in patients bridged to transplantation with the Thoratec VAD device: A single-center retrospective study on more than 100 patients. J Heart Lung Transplant 2000: 19: 964-968.
115. Loebe M, Hennig E, Muller J, et al. Long-term mechanical circulatory support as a bridge to transplantation, for recovery from cardiomyopathy, and for permanent replacement. Eur J Cardiothorac Surg 1997; 11(Suppl.): S18-S24.
116. Williams MR, Oz MC. Indications and patient selection for mechanical ventricular assistance. Ann Thorac Surg 2001; 71(Suppl.): S86-S91.
117. Potapov EV, Hennig F, Wagner FD, et al. Natriuretic peptides and E-selectin as predictors of acute deterioration in patients with inotrope-dependent heart failure. Eur J Cardiothorac Surg 2005; 27: 899-905.
118. Lamour JM, Kanter KR, Naftel DC,et al; Cardiac Transplant Registry Database; Pediatric Heart Transplant Study. The effect of age, diagnosis, and previous surgery in children and adults undergoing heart transplantation for congenital heart disease. J Am Coll Cardiol. 2009;54(2):160-165.
119. Kirk R, Edwards LB, Aurora P, et al. Registry of the International Society for Heart and Lung Transplantation: eleventh official pediatric heart transplantation report–2008. J Heart Lung Transplant 2008;27: 970–977.
120. Rao V, Oz MC, Flannery MA, et al. Revised screening scale to predict survival after insertion of a left ventricular assist device. J Thorac Cardiovasc Surg. 2003;125(4):855-862.
121. Oz MC, Goldstein DJ, Pepino P, et al. Screening scale predicts patients successfully receiving long-term implantable left ventricular assist devices. Circulation. 1995;92(9 Suppl):II169-71.

9. Publication list

1. Fan Y, Zhang AM, Xiao YB, Weng YG, Hetzer R. Glucose-insulin-potassium (GIK) therapy in adult patients undergoing cardiac surgery: a meta-analysis. Eur J Cardiothorac Surg. 2010 Nov 12. [Epub ahead of print]

2. Fan Y, Weng YG, Xiao YB, Huebler M, Franz N, Potapov E, Hetzer R. Outcomes of ventricular assist device support in young patient with small body surface area. Eur J Cardiothorac Surg. 2010 Sep 28. [Epub ahead of print]

3. Fan Y, Zhang AM, Xiao YB, Weng YG, Hetzer R. Warm versus cold cardioplegia for heart surgery: a meta-analysis. Eur J Cardiothorac Surg. 2010 Apr;37(4):912-9. Epub 2009 Oct 21.

4. Fan Y, Xiao YB, Weng YG. Tacrolimus versus cyclosporine for adult lung transplant recipients: a meta-analysis. Transplant Proc. 2009 Jun;41(5):1821-4.

5. Fan Y, Xiao YB, Weng YG, Hetzer R. Tacrolimus versus cyclosporine microemulsion for heart transplant recipients: a meta-analysis. J Heart Lung Transplant. 2009 Jan;28(1):58-66. Epub 2008 Dec 4.

10. Acknowledgement

My first heartfelt thanks was given to Prof. Dr. Roland Hetzer, Leiter Professor des Deutschen Herzzentrums Berlin and Aerztlicher Direktor der Abteilung fuer Herz-, Thorax- und Gefaesschirurgie, for his generously offering the opportunity to be a guest surgeon and the doctoral project to me in his institute. Only with his continuous support and encouragement I could complete this work successfully.

I wish to express my thanks to Prof. Dr. Yu-Guo Weng for his guide in my research and help in data collection. I never forget his kind help and care in my work and life.

I extend my sincere thanks to Dr. Evgenij Potapov for his excellent assistance in my work; his instruction was part of this work.

I would like to thank Anne Gale, Editor in the Life Sciences (ELS), for her excellent editorial assistance in my work.

I would like to thank Dr. Jian Sun for his valuable suggestions and cooperation.

I devote this paper to my wife, whose wonderful work on the statistic analysis of the results is also a part of this paper. I am grateful to my parents for their help and support to my study in Germany and my family.

11. Curriculum Vitae

CV is not available online for private reason.

12. Erklärung

Ich, Ye Fan, erkläre, dass ich die vorgelegte Dissertation mit dem Thema: “Clinical Analysis and Preoperative Predictors of Survival in Children after Ventricular Assist Device Implantation“ selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.

Datum **Unterschrift**