Diplomarbeit

Expiriences with Berlin Heart Excor BiVentricular support in children
BVAD Excor use in children

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Zusammenfassung

„Erfahrungen mit dem Berlin Heart Excor als biventrikuläres Herzunterstützungssystem im Kindesalter“

Hintergrund. Bei Kindern im terminalen Herzversagen spielt die Therapie mittels mechanischer Kreislaufunterstützung eine wichtige Rolle, weil die Knappheit von Spenderorganen zu langen Wartezeiten auf eine Herztransplantation führt. Wir berichten über unsere Zentrumsergebnisse mit dem Berlin Heart EXCOR® (Berlin Heart AG, Berlin, Germany), einem paracorporalem biventrikulären Unterstützungssystem.

Methode. Zwischen 2006 und 2012 wurden 9 BVAD Excor Implantationen an der Medizinischen Universität Graz betreut; darunter waren vier Kinder (6a, 14a, 14a, 17a, alle männlich). Grunderkrankungen waren: postcardiotomy heart failure n:1, dilatative Kardiomyopathie n:2, Herzinsuffizienz unklarer Genese n:1. Die Analyse erfolgte retrospektiv, Ausschlusskriterien waren ein Alter über 18 Jahre, LVADs sowie nicht Excor BVADs.

Ergebnisse. 30 Tage Mortalität war 25% (n:1, Blutung), ein weiteres Kind verstarb nach 84 Tagen am BVAD auf Grund einer Hirnblutung (INR 5.5; T-ASS). Mittlere BVAD Unterstützungsdauer war: 223.75 Tage (4 Tage, 84 Tage, 262 Tage, 545 Tage). Pumpenkopfwechsel waren bei zwei Kindern auf Grund von Thrombenbildungen nötig: 109 (linke Kammer) und 185 Tage (rechte Kammer). Bei einem Patienten kam es zu einer teilweisen Membranruptur der rechten Kammer, sodass diese nach 298 Tagen getauscht werden musste. Weitere ernstzunehmende Komplikationen im Langzeitverlauf waren Driveline-Infektionen (n:2), welche eine i.v.Antibiose benötigten, sowie rezidivierende Epistaxis (n:3), welche konservativ behandelt wurden. Zwei Kinder wurden nach 262/545 am BVAD erfolgreich transplantiert (HTx). Wartezeit auf der HU Liste waren: 480 und 242 Tage. Sie konnten nach der HTx nach Hause entlassen werden. Follow up ist 1.9 (715d) und 2.3 (850d) Jahre nach HTx.

Diskussion. Das Auftretetn häufiger Komplikationen, wie Thrombenbildung und Blutungskomplikationen, sowie Driveline Infektionen sollte verringert werden, um die Lebensqulität und das Überleben nach BVAD Implantationen zu steigern.

Abstract

"**Experiences with Berlin Heart Excor BiVentricular support in children"**

Background. In children diagnosed with chronic cardiomyopathy (CMP) mechanical circulatory support (MCS) plays an increasingly important role, especially because the shortage of suitable donor hearts leads to increased waiting times on the transplant waiting-list. We report our experiences with the paracorporal Berlin Heart EXCOR® (Berlin Heart AG, Berlin, Germany) used as biventricuclar assist device (BVAD).

Method. Between 2006 and 2012 9 BVAD Excors were implanted at the Medical University Graz; 4 of them in children (6a, 14a, 14a, 17a, all of them male). Underlying diseases were: postcardiotomy failure n:1, dilatative cardiomyopathy n:2, heart failure of unknown origin n:1. The analysis was done retrospectively, exclusion criteria have been defined as age over 18 years, LVADs and non Excor BVADs.

Results. 30 day mortality was 25% (n:1, hemorrhage), another child died after 84 days on BVAD support because of brain hemorrhage (INR 5.5; T-ASS). Mean duration time of BVAD support were 223.75 days (4 days, 84 days, 262 days, 545 days). In two children pump head replacement was needed because of thrombus formation: after 109 days (left chamber) and after 185 days (right chamber). One patient had a fractional rupture of the membrane surface of the right chamber that required pump head exchange after 298 days. Further severe complications in the long-term course were two drive-line infections, which required i.v. antibiosis, as well as recurring epistaxis in three children, treated conservatively. Two children were successfully transplanted. Waiting time on high urgent list was: 480 and 242 days. Both were discharged successfully. Follow up time is 1.9 (715days) and 2.3 (850days) years after HTX.

Discussion. The occurrence of frequent complications, like thrombus formation and hemorrhage complications as well as drive-line infections should be reduced in order to enhance quality of life and survival after BVAD implantation.

Contents

Glossary, list of abbreviations

ACE-inhibitors	angiotensin-converting enzyme inhibitors
ACT	activated clotting time
AKH-hospital	general hospital
aPTT	activated partial thromboplastin time
ARDS	acute respirators distress syndrome
ARA	arachidonic acid
ATP-ase	adenosine triphosphatase
AT III	antithombin III
bili	bilirubin
BMI	body mass index
BNP	brain natriuretic peptide
BSA	body surface area
BTD	bridge to destination
BTR	bridge to recovery
BTT	bridge to transplantation
BVAD	biventricular assist device
ß-TG	beta-thromboglubolin
ß-blockers	beta-blockers
cm	centimetre
CMV	cytomegalovirus
Cont.	continuous
CPB	cardiopulmonary bypass
crea	creatinine
CRP	C-reactive protein
CT	computer tomography
cvp	central venous pressure
Cyclic-CAMP	cyclic adenosine monophosphate
DCM	dilated cardiomyathy
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECMO	extracorporal membrane oxygenation
EF	ejection fraction

G/l	gram per litre
hb	hemoglobin
hkt	hematokrit
HIT II	heparin-induced thrombocytopenia type II
HTx	heart transplantation
HU	high urgent
HVAD	Heartware ventricular assist device
IABP	intraaortic balloon pump
ICU	intensive care unit
INR	international normalized ratio
Intra.	Intracorporal
IU/kg	international unit per kilogram
IU/kg/h	international unit per kilogram per day
i.v.	intra venous
kg	kilogram
LDH	lactatdehydrogenasis
l/min	litre per minute
LVEDD	left ventricular end-diastolic diameter
LVAD	left ventricular assist device
m	month
m^2	square meter
map	mean arterial pressure
MCS	mechanical circulatory support
mean BP	mean blood pressure
mg/d	milligram per day
mg/dl	milligram per decilitre
mg/kg/d	milligram per kilogram per day
mm	millimetre
mmHg	millimetres of mercury
MRI	magnetic resonance imaging
µg/kg/min	microgram per kilogram per minute
NO	nitric oxide
NYHA	New York Heart Association
Para.	paracorporal

PCMR	Pediatric Cardiomypathy Registry
PF4	platelet factor 4
pg/ml	picogram per millilitre
pHTx	pediatric heart transplantation
PO2	partial pressure of oxygen
PCO2	partial pressure of carbon dioxide
rpm	revolutions per minute
PLTs	platelets
Puls.	pulsatile
RVAD	right ventricular assist device
SIR	systemic inflammatory response
SIRS	systemic inflammatory response syndrome
s-p-P	serum pro brain natriuretic peptide
tci	tricuspid insufficiency
TAH	total artificial heart
TAT	thrombocyte aggregation test
TEE	transoesophageal echocardiography
TEG	thrombelastography
TI	tricuspid insufficiency
TIA	transient ischemic attack
U/l	unit per litre
VAD	ventricular assist device
VADs	ventricular assist devices
ys.	years

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1 Introduction

1.1 General introduction

In the first part of the following introduction the causes, as well as medical therapy of terminal heart failure in children will be discussed. In the second part the mechanical circulatory support, which is needed as bridge to either bridge, recovery or transplantation, will be reviewed. The Berlin Heart Excor will be explained in depth (Berlin Heart AG, Berlin, Germany), a paracorporal pneumatically driven biventricular assist device.

1.2 Heart failure in children

1.2.1 Definition

Heart failure in children is a progressive clinical and pathophysiological syndrome caused by cardiovascular and noncardiovascular abnormalities, which are resulting in characteristic signs, and symptoms including edema, respiratory distress, growth failure, exercise intolerance and is accompanied by circulatory, neurohumoral and molecular derangements. (7) In adults heart failure remains much more common with 280.000 death per year in the United States, but in children heart failure is highly lethal with 46% either dying or undergoing heart transplantation (HTx). (8)

1.2.2 Epidemiology

Compared to adults there are few studies including epidemiological data about heart failure in children. Two Universities, the University Children's Hospital Essen in Germany and the University of Liege in Belgium, performed epidemiological studies on heart failure in children over a period of ten years. (9,10)

Essen included 1755 patients in their study between 1989 and 1998 and reported a cumulative incidence of congestive heart failure (CHF) of 334 out of 1000 patients and a prevalence of 279 in 1000 with all heart diseases. *"Mortality: during the 10-year interval 111 out of 1,755 patients with heart diseases died, 81 of them for CHF. This gives an*

overall mortality of 6.3%, 18% following heart surgery or cardiac catheterization, 74% with signs of CHF." (10)

Liege included 1196 children with heart disease in their study between 1996 and 2006.

"Heart failure occurred in 124 of these patients (10.4%): 64 out of 1,031 children with congenital heart diseases (6.2%), 13 out of 96 children with rhythm or conduction disturbances (13.5%), 23 out of 39 children with acquired heart diseases (59.0%), and 24 out of 30 children with cardiomyopathies (80.0%). Heart failure occurred in 72 cases (58.1%) during the first year of life." "The mortality associated with HF and its cause was also lower for children with congenital heart disease (4.7%) than for the other cardiac conditions (8.7%, 23.0%, and 25.0%, for acquired heart diseases, rhythm disturbances, and cardiomyopathies, respectively)." (9)

The most frequent cause for heart failure with a structural normal heart leading to heart transplantation in children above one year of age is cardiomyopathy. Since 1994 the Pediatric Cardiomypathy Registry (PCMR) has been documenting and analysing over 3500 cases of North American children with cardiomyopathy. (11)

„Early analyses determined estimates for the incidence of pediatric cardiomyopathy (1.13 cases per 100,000 children per year), risk factors for cardiomyopathy (age less than 1 year, male sex, black race, and living in New England as opposed to the Central Southwestern states), the prevalence of heart failure at diagnosis (6%–84% depending on cause), and 10-year survival (29%– 94% depending on cause)." (11)

These results are similar to those reported for Finland and Australia. (8,12,13)

1.2.3 Etiology (1)

In childhood heart failure is often caused by volume or pressure-exposure in consequence of congenital heart defects. Heart failure is rarely caused by primary myocardial heart insufficiency to wit deficient myocardial contraction as a result of reduced cell number in contraction elements at cardiomyopathy, arterial hypertension, tachy-or bradycardial dysrhythmia or metabolic imbalances.

Volume overload	Left-to-right shunting	Ventricular septal defect
		Patent ductus arteriosus
	Atrioventricular or semilunar valve insufficiency	Aortic regurgigation in bicommsural aortic valve
		Pulmonary regurgigation after repair of tetralogy of Fallot
Pressure overload	Left sided obstruction	Severe aortic stenosis
		Aortic coarctation
	Right sided obstruction	Severe pulmonary stenosis
Complex congenital heart disease	Single ventricle	Hypoplastic left heart syndrome
		Unbalanced atrioventricular septal defect
	Systemic right ventricle	L-transposition (“corrected transposition”) of the great vessels

Table 1 - Congenital malformations, adapted from Daphne T. Hsu and Gail D. Pearson (7)

Primary cardiomyopathy	Dilated
	Hypertrophic
	Restrictive
Secondary cardiomyopathy	Arrhythmogenic
	Ischemic
	Toxic
	Infiltrativ
	Infectious

Table 2 - Structurally normal heart, adapted from Daphne T. Hsu and Gail D. Pearson (7)

1.2.4 Pathophysiology (1)

With cardiac insufficiency different neurohumoral mechanisms are activated, especially the renin-angiotensin-aldosteron system and the sympathetic tone. Through the mechanism of higher sodium, chloride and water reabsorption increased aldosteron production leads to high intra-vascular volume and high blood pressure in the systemic and pulmonary circulation. Consequently this increase in preload in an early stage of heart failure is useful to improve the cardiac output because in this way the heart's contraction force is enhanced by the Frank-Starling-Mechanism. The enlargement of the ventricle causes increased wall tension with enhanced myocardial oxygen consumption. Finally this increased preload leads to symptoms of congestion in the pulmonary or systemic circulation.
The amplified production of angiotensin II as well as the increased sympathic tone lead to arterial vasoconstriction which results in an increase of system resistance (afterload) and consequently to this to decreased stroke volume. Furthermore the aggravated sympathic tone increases the myocardial oxygen consumption, as mentioned before, which leads to down-regulation of ß-receptor-density due to chronic activation.

1.2.5 Classification

In adults the different classes of cardiac insufficiency are classified by the well-established NYHA (New York Heart Association). Analogously to this classification there is a modified system, the Ross Heart Failure Classification for Children.

Class I	Asymptomatic
Class II	Mild tachypnea or diaphoresis with feeding in infants Dyspnoe on exertion in older children
Class III	Marked tachypnea or diaphoresis with feeding in infants Marked dyspnoe on exertion Prolonged feeding times with growth failure
Class IV	Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest

Table 3 - Modified Ross Heart Failure Classification for children, adapted from Daphne T. Hsu and Gail D. Pearson (7)

1.2.6 Clinical diagnostics

Based on the multifactorial pathogenesis of heart failure in children, different tests had to be run to diagnose the syndrome heart failure.

1.2.6.1 Symptoms

Severe symptoms of heart failure are growth failure, respiratory distress and exercise intolerance unrelated to the cause of heart failure. (7,14) In case of right heart failure as with single ventricle physiology, tetralogy of Fallot or Ebstein anomaly, the core symptoms are systemic venous congestion, decreased exercise capacity and increasing hypoxemia. (7,14) In patients with functional single ventricle physiology, after Fontan-operation, protein-loosing enteropathy is a severe sign of heart failure. (7,14)

1.2.6.2 Echocardiography

In pediatric cardiology echocardiography is the first imaging used to detect structural and functional details of the heart, especially ventricular size and function, whereat the left ventricle is easier to evaluate than the right ventricle or a single ventricle heart. (14)
Poor ejection fraction and fractional shortening at time of first presentation in children with dilated cardiomyopathy (DCM) have been connected to a worse outcome. (8,15) Furthermore, correlation has been shown between a more spherical shape of the left ventricle following left ventricular remodeling and worse outcome. (14,16)
In cases of single ventricle anatomy or right ventricle dysfunction the Doppler myocardial performance index is useful to asses the ventricle's function. (17,18)

1.2.6.3 Electrocardiogram (ECG) (2)

The ECG shows the electrical activity of the heart muscles and permits certain assertions regarding transitions disturbances and arrhythmias. Furthermore certain ECG signs may indicate cardiac hypertrophy, signs of increased myocardial perfusion, myocardial injury and abnormal anatomical position of the heart.

1.2.6.4 Exercise testing

Unlike to adults exercise testing according to oxygen saturation is very difficult in children with heart failure due to the fact that oxygen saturation of these children depends on the underlying disease of heart failure and age, which makes oxygen consumption difficult to interpret. (14) For those reasons energy expenditure during feeding is an informal test, more over growth failure is often an indication to intervene. (14)

1.2.6.5 Laboratory parameters

High levels of adrenalin, noradrenalin, liver enzymes, bilirubin, urea, creatinin and low levels of protein and sodium in plasma concentration are significant for heart failure. (3) A BNP (brain natriuretic peptide) level >300 pg/ml has been shown to be strongly correlated to poor outcome and to predict death, transplantation or hospitalization because of heart failure. (19)

Further significance is give to the occurrence of high specific gravity in urine with increased secretion of proteins and catecholamines and decreased secretion of sodium. (3)

The blood gas analysis shows a respiratory acidosis, decreased arterial PO2 (partial pressure of oxygen) and an increased PCO2 (partial pressure of oxygen), which leads to lactat acidosis and thereby to mixed respiratory-metabolic acidosis. (3)

1.2.6.6 X-Ray (3)

Solid signs of heart failure are dilatation of the individual heart segments with additional pulmonary edema.

1.2.6.7 Intracardiac catheter (4)

With right-and left-heart catheter it is possible to measure pressure and oxygen saturation in achieved cavities of the heart and large blood vessels. Stenoses in the area of heart valves, large blood vessels and valve insufficiency are detected by heart catheterization by pressure receptors. Oxygen saturation is measured in percent with collected blood samples or intravascular or intracardial catheter. The method for determination of oxygen saturation

is useful to detect intracardial or aortopulmonary defects with right to left or left to right shunts and gives an indication of the defect's size.

1.2.6.8 Further diagnostics

For even more precise clarification non-invasive diagnostics like long-term ECG, long-term blood pressure assessment, pulmonary function test, magnetic resonance imaging (MRI) and invasive diagnostics like endomyocardial biopsy and electrophysiological tests may be used in addition.

1.2.7 Treatment

Heart failure in children is rare but therefore decisive for their fate. In children heart failure is often caused by congenital heart disease rather than acquired heart disease. The treatment of heart failure in children is based on pathogenesis, aetiology and symptoms.

1.2.7.1 Medical therapy

In the following paragraphs the substance groups of medical treatment of heart failure in children are discussed because of their importance as therapy before and during mechanical circulatory support.

Digitalis glycosides (20)**.** So far digitalis glycosides are the only inotropic substance for long time use to treat heart failure in children. Its efficacy is based on the inhibition of the potassium/sodium ATP-ase. The combination therapy with diuretics promotes the transmembrane exchange of potassium and sodium and the positives effects of digitalis, which is also improved with a relief of volume. The negative chronotrope effect economizes the oxygen and energy consumption of the heart.

Catecholamines (20)**.** Catecholamines are used to treat acute heart failure. Phosphodiesterase inhibitors as well as sympathomimetics are leading to higher mortality in chronic heart failure. However, if needed, catecholamines in intermittent or continuous application form are often needed to treat temporarily acute heart failure.

Dopamine has no foreseeable effectiveness concerning the correlation of dosage and hemodynamic effects because of a high variability of dopamine-clearance, protein binding

and dopamine-metabolism. Although dopamine's inotropic effect is reduced in newborns and infants, it is the medicine of choice to treat acute heart failure in children.

The main effect of synthetic catecholamine dobutamine is an increasing of the heart's contractility. Its effectiveness is presents an age-dependent dose-response curve. In combination with phosphodiesterase inhibitors it is used to treat acute heart failure while preserving adequate myocardial perfusion pressure.

The endogenous produced catecholamine adrenaline is used to treat "low cardiac output" in cases of septic shock, after cardiac surgery and after cardiopulmonary resuscitation or when other inotropic therapy fails. Treating "low cardiac output" in newborns with adrenalin, results in increased cardiac output per minute, heart rate and blood pressure, achieving constant or even decreased pulmonary and systemic vascular resistance.

In case of inadequate renal perfusion pressure adrenalin and noradrenalin can establish an adequate renal perfusion pressure, leading to improved renal perfusion, renal performance and urinary excretion.

In conclusion, intra-venous catecholamines should be dosed precisely depending on hemodynamic effects and should be administered as short as possible.

Phosphodiesterase inhibitors (20)**.** The mechanism of action is to inhibit the phosphodiesterase III, that makes the breaking down of cyclic-CAMP slow down which leads to increased calcium concentration in the heart muscle and reduced calcium concentration in the vascular muscle.

Approved phosphodiestase inhibitors for acute heart failure treatment in children are Amrinone, Milrinone and Enoximone. Because of causing thrombozytopenia, Amrinone is hardly used. Enoximone is suitable for single dose or continuous infusion whereas Milrinone is only applied by infusion.

Combination therapy with catecholamines and phosphodiesterase-inhibitors reduces undesired side effects of single catecholamine therapy (downregulation of beta-receptors) by shortening treatment times with catecholamines.

ACE-inhibitors (20)**.** The mechanism of action is to inhibit the angiotensin-converting enzyme (ACE), avoiding formation of angiotensin II out of angiotensin I. The effects are: reduced systemic resistance, increased venous capacity, decreased aldosteron secretion, increased potassium secretion and increased renal blood flow. ACE-inhibitors approved for treatment of chronic heart failure in children are Enalapril and Lisinopril in combination with approved ß-blockers Atenolol, Metoprolol, Carvedilol. These are used to reduce ACE-inhibitor caused hyperreninism.

Nitrates (20)**.** Nitrates are used to treat acute heart failure with sufficient myocardial perfusion pressure by dosage related response reduction of the heart's preload. Advantages of nitrates are relieving the heart's burden by increasing the cardiac output per minute and are used in combination with inotropics to decrease myocardial oxygen consumption while improving quality of peripheral and pulmonary perfusion.

Diuretics (20)**.** Diuretics should only be used in context of assessing the kidney's function, because diuretic therapy leads to an increased neurohumoral response in case of intra-arterial lack of volume.

1.2.7.2 Surgical and device therapy

There are quite a number of opportunities with interventional and surgical techniques. (10) Congenital heart surgery has evolved enormously over the past decades. (21) At the beginning 40% operative mortality was reported which is by current standards unacceptable, but in the context of that area where the only alternatives were palliative shunt or an unfavourable natural history, this was still a huge improvement. Today even children with terminal heart failure without any option than natural history of the disease back at the early time of congenital heart surgery may face surgical options for cure. (22)

If terminal heart failure has occurred besides optimal medical therapy paediatric heart transplantation (pHTx) remains the treatment of choice with excellent survival rates after three years. (23,24) However there is only a limited availability of paediatric donor organs and the increasing donor shortage prolongs waiting time resulting in a high rate of death among children on the pHTx waiting list. In 2011 the mean waiting time within the Eurotransplant region was 322 days for patients under 5 years of age. (25); even if international donor exchange is trying to overcome this shortage (26), death on the waiting list is still high. (27) To overcome death during the waiting time, bridge to transplantation (BTT) with mechanical circulatory support (MCS) has been established. (28) Until recently, in the United States, the DeBakey VAD child (MicroMed Technology Inc., Houston, TX) was the only Food and Drug Administration approved VAD (ventricular assist device) designed for use in children, but its approval was limited to children aged older than five years and with a body surface area (BSA) greater than 0.7 m^2. (29) In Europe the Berlin Heart offers mechanical circulatory support even in newborns. (30)

1.3 Mechanical circulatory support systems in children

1.3.1 Historical development of assist devices

In 1963 the first mechanical heart pump was used after a heart surgery by Stanley. (31) One year later Hardy and his group did the first heart transplantation in a man with a large chimpanzee heart. (32) The first heart transplantation with a human heart was done by Bernard and his group in 1967. (33) From this point on it was possible to treat terminal heart failure. Another year later Denton Cooley implanted the first artificial heart instead of the original heart. (31) In 1967 DeBakey used a left-atrial to axillary artery VAD to recover a 16-years-old girl suffering from postcardiotomy failure after mitral replacement. (34) During the following decades, modifications of the original 'heart-lung-machine' like ECMO (extracorporal membrane oxygenation) or extracorporal centrifugal pumps have been the principal art of cardiac support. Generally the mechanical assist devices of the first generation were big, worked with pulsatile blood flow and had many technical problems. Because of the lack of donor organs a huge evolvement of mechanical assist devices appeared. In the 90ties continuous blood flow pumps were developed and on the 13th of November in 1998 the first continuous blood flow pump was implanted by the German Heart Center Berlin, hence the Vienna AKH-hospital (general hospital) followed. (31)

In 1976 Bartlett presented his experience with thirteen dying children, in respiratory distress after heart operation, that were treated with ECMO. (35)

In 1978 the first experiences with the use of intraaortic balloon pump (IABP) in children were made. Pollock et al. reported on 14 children, who received IABP after open-heart surgery. All children under the age of five died and there were six long-term survivors. (36)

In 1985 Jack G. Copeland implanted the first total artificial heart, a Jravik-7, successfully. After 9.5 days of support this patient was heart transplanted. Since 1993 the group around Jack G. Copeland implanted more than 960 artificial hearts, type SynCardia/West® (SynCardia Systems, Tucson, Ariz., USA). (37)

The first implantation of a mechanical assist device in children took place in 1989 and was conducted by Frazier. The patient was a nine year old boy and was successfully bridged to heart transplantation with a Biomedicus (Medtronic, Eden Prairie, MN) centrifugal pump. Supporting time was twelve hours. In 1990 the first Berlin Heart Excor, in adult size (50-

ml), was implanted in a nine years old child for one week with an uneventful postoperative time after heart transplantation. Two years later, in 1992, pumps in sizes 10-ml, 25-ml and 30-ml have been devised and the 10-ml pump was implanted in a 12-month-old child. (38)
In 1994 the first Medos VAD (Medos Medizintechnik GmbH, Stolberg, Germany) was implanted successfully as bridge to transplantation. (39)

1.3.2 Reflecting the use of ventricular support in children

Starting with the IABP different types and concepts for MCS have been established. The mainstay for support in small children has been extracorporal membrane oxygenation (ECMO), offering lung and circulatory support (see 2.2.1). This is limited though to a support time of 10 to 20 days before serious complications occur. This support time may be too short for adequate bridge to transplantation (BTT) as waiting times are often more than 100 days. (40)
Due to the limited availability of pediatric donor organs the waiting time for heart transplantation (HTx) is increasing. In 2011 the mean waiting time in the Eurotransplant [ET] region was 322 days for patients under 5 years of age. (25)
In 1989 Frazier implanted a mechanical assist device in a nine year old boy who was successfully bridged to heart transplantation with a Biomedicus (Medtronic, Eden Prairie, MN) centrifugal pump; supporting time was twelve hours. In 1990 the first Berlin Heart EXCOR, in adult size 50-ml pump, was implanted in a nine year old child for one week with an uneventful postoperative time after heart transplantation. (41) Two years later, in 1992, pumps in sizes 10-ml, 25-ml and 30-ml were devised and the 10-ml pump was implanted in a 12-months-old child. (42) Two years later the first Medos VAD (Medos Medizintechnik GmbH, Stolberg, Germany) was implanted successfully as bridge to transplantation. (43)
Contrary to the total artificial heart, which replaces the native heart, VADs support the heart, but the native heart is left in place at the time of operation. Due to their size intracorporal devices are only used in grown up children except the Heartware (HVAD). The experience with this third generation continuous flow LVAD was reported by the Berlin group (44) and may be used in children weighing 16 kilograms or more. This device may also be used in single ventricular circulation as reported by Hübler et al. (45); nevertheless in biventricular heart failure needing mechanical support for both ventricles this device is also not a valid option. The only possibility for BVAD in small children is

the Berlin Heart EXCOR device using paracorporal pump chambers. The Thoratec PediVas pump system, whose design was modified from the CentriMag (Levitronix, Waltham, MA), has been developed to meet the physiological requirements of young paediatric and neonatal patients. The PediVAS was evaluated in 14 paediatric animals for up to 30 days, demonstrating acceptable hydraulic function and hemocompability. (46)

1.3.3 Distinguishing features of ventricular assist devices (5)

Ventricular assist devices (VAD) supporting the left (LVAD), the right (RVAD) or both ventricles (BVAD) have emerged as the standard of care for patients with advanced heart failure. Initially used to bridge patients to transplantation (BTT) they are now more frequently used as permanent support in adults (bridge to destination, BTD). Bridge to recovery (BTR) especially as long-term support might be a valid option for only a small number of patients but is well established in postcardiotomy heart failure. Although there are different devices available, patient selection, pre-and intraoperative preparation, and timing of VAD implant are important elements critical to successful circulatory support.
Ventricular assist devices (VADs) can be classified as follows.
VADs are used as short-term support (days to weeks) in cases of fulminant myocarditis with consecutive reversible cardiac insufficiency and in case of postcardiotomy heart failure, as mentioned before. For intermediate to long-term support (weeks to months) VADs are indicated in case of chronic heart failure due to congestive or acquired heart disease as bridge to transplantation (BTT). Dependent on the manner of cannulation of the native ventricular system VAD support is named “in series” or “in parallel”. “In series” means inflow to the device is provided by cannulation of the ventricular apex and outflow from the device is given through cannulation of the related great vessel. “In parallel” support inflow to the device is provided by cannulation of the related feeding vessel of the supported ventricle, outflow cannulation is managed in the same manner as outflow cannulation of “in series” support. Advantages of “in series” support are reduced native enddiastolic diameter and reduced endsystolic wall stress of the native ventricle as a result of a low-impendance outflow to the device from the ventricle. Consequently satisfactory decompression of the ventricle is often achieved and therefore the risk of thrombosis and cerebral infarcts is reduced. Cannulation of the ventricle’s apex may lead to akinesia or dyskinesia in this area, which is disadvantageous for patients with recovering heart function, but does not matter for patients who are planned for heart transplantation.

Additionally VADs have to be distinguished in paracorporal and intracorporal devices. Paracorporal devices are located outside the body; consequently the inflow and outflow conduits have to penetrate the body's surface area. Intracorporal assist devices are implantable and therefore placed in the patient's pericardial cavity or preperitoneally, hence implantation of intracorporal assist devices is impaired by a body surface area <1.5 m^2. Depending on the kind of the pulsatile assist device different operating modes can be applied. "Manual mode" (single-stroke mode) is used for de-airing of the system during operation. In "asynchronous mode" the pump is set at a fixed rate (beats per minute) independent of the native ventricle's ejection fraction. Consequently in "asynchronous mode" the stroke volume is dependent on the pumping rate. In "volume mode" (fill to empty) the pumping mechanism is triggered by predetermined filling volume of the device. According to this, a VAD's ejection fraction depends on the VAD's preload and the variable pumping mechanism. In "synchronous mode" the ECG's R-wave is usually determined to trigger the VAD's ejection. "Adjustable delay mode" is used to reduce the ventricle's afterload by avoiding the device's and native ventricle's ejection at the same time. Another advantage of "synchronous mode" is the possibility to program the percentage of the systole, leading to an increased rapidity of the ejection phase. As a result of the slow ejection phase the damage to blood cells is reduced.

1.3.4 Pediatric ventricular assist devices (pVADs)

The **extracorporal membrane oxygenation (ECMO)** therapy is commonly used for cardiac circulatory support, respiratory support or both when lungs and heart fail.

In cases of intracardiac defects and also respiratory failure and unknown possibility of recovery from shock-induced organ dysfunction, ECMO is quickly accessible in many cardiac centres. To allow complete cardiac depression, ballon atrial septostomy or left atrial venting can be established. ECMO therapy only provides short-term support, because within two to three weeks of support fatal complications appear, such as hemorrhage, cerebral events and infection, leading to worse outcome. (39)

Nonetheles ECMO affords an effective primary therapy option in cases of acute heart failure, as bridge to decision (BTD), bridge to transplantation (BTT), bridge to recovery (BTR) or bridge to bridge (BTB) when another mechanical assist device for long-term support is needed. (47)

The ECMO is inserted in large vessels, venous-venous in cases of lung failure (e.g. acute respiratory distress syndrome, ARDS) or venous-arterial in case of heart failure (e.g. acute, chronic heart failure, resuscitation, end-stage cardioyopathy, et cetera). This system consists of a roller pump with a small pre-processing venous reservoir or centrifugal pump for blood circulation, a membrane oxygenator for gas exchange and a heat exchanger for blood warming before entering the patient again. Cannulation is done peripheral in the right internal jugular vein and the common carotid artery or central, meaning transsternal in the right arterial appendage and aorta in case of post-cardiotomy heart failure. Complications as mediastinal bleeding and infection must be well considered. Anticoagulation is achieved by heparin-coated surfaces to reduce surface-induced complement activation and platelet dysfunction. Positive aspects of ECMO are relative ease of use, wide availability, potential for rapid stabilization, perpheral cannulation, capability of biventricular support, adjustment for each body height and weight, effective oxygenation, and wide experience in pediatric use. Negative aspects of ECMO use are its requirement of blood prime, extensive anticoagulation, nonpulsatile flow, decreased pulmonary blood flow, bleeding complications and high incidence of neurological complications. (47)

The **intraaortic balloon pump (IABP)** provides an option to temporarily treat acute heart failure in children and is indicated in the setting of reversible heart failure despite maximum inotropic support or after surgical correction of congenital heart defects. This system consists of an expandable balloon placed in the descending aorta by catheterization attached to a control console outside the body. The balloon is periodically inflated in diastole and deflated at the onset of systole. Deflation reduces the left ventricle's afterload and therefore improves ventricular function. Inflation raises the intraaortic diastolic pressure and consequently coronary perfusion pressure is increased. Therefore the heart's oxygen consumption is reduced and the cardiac output is increased leading to improved heart and brain circulation. Important factors to consider for IABP use in children are the elasticity of the pediatric aorta altering the force of diastolic augmentation, and a high heart rate often combined with a high incidence of arrhythmia making the timing of in-and deflation very difficult. The IABP use in children should be well considered because of the high complication rate. (48)

Commonly used **centrifugal assist devices** are the BioMedicus Biopump® (Medtronic, Minneapolis, MN), the CentriMag® (Levitronix, Zürich, Switzerland), the RotaFlow® (Maquet, Hirrlingen, Germany), the Capiox® (Terumo, Ann Arbor, MI) and TandemHeart

pVAD® (CardiacAssist, Inc. Pittsburgh, Pennsylvania), for use in children as shown in table 4. The centrifugal assist device is designed for short-term cardiac support, either for the left, right or both ventricles. (39) The nonpusatile centrifugal working pump is used for cardiopulmonary bypass, ECMO or ventricular assistance. (47)

This system is built on rotating components creating a vortex to pump asynchronous continuous blood. (49) Magnetically controlled pump capacity is 5-6 l/min caused by turbine spins of 10,000-20,000 rpm. (39) Circulatory pump systems work independently from volume and native heart contraction. (49) Cannulation is done in the left atrium and the ascending aorta for left heart support or in the right atrium and the pulmonary artery for right heart support. (47)

Most common complications are bleeding, thrombosis and infection, followed by blood trauma and neurological events. (39) Anticoagulation is ensured by heparin coated surfaces and systemic anticoagulation with heparin. (47)

Positive aspects of centrifugal pumps are less trauma to blood cells and less frequent inflammatory response compared to other assist devices, furthermore less air entrainment, ease of use, ease of implantation, fast set up time, low priming volume, low-level of anticoagulation and low costs. (39,47,49) Negative aspects of this system are shorter supporting time and thrombus formation. (47) Furthermore in many cases the thorax must be left open, requiring sedation and mechanical ventilation. (39)

In cases of short-term ventricular support without compromised lung function, if recovery can be achieved in two weeks, the centrifugal pump could be a good choice for support. (39)

Axial flow VADs are light, small, implantable, quiet assist devices for long-term outpatient support. Therefore axial flow pumps are used for BTT and BTD. Different types of axial flow devices are the MikroMed DeBakey VAD® (MicroMed Technology, Inc., Houston, TX), the HeartMateII® (Thoratec, Pleasanton, CA), Jarvik2000® (Jarvik heart, Texas Heart Institute, Houston, TX) and the INCOR VAD® (Berlin Heart, Berlin, Germany), for use in children as can be seen in table 4. This pump consists of a magnetically driven levitated impeller that rotates in a cylindrical chamber and is placed in the left or right ventricle through a catheter. The operating mode is asynchronous and a diffuser at the pump's exit minimizes the turbulence of the blood flow. (49)

Continuous flow systems facilitate the heart's function, allowing meaningful cardiac contraction. Furthermore these systems provide good end-organ perfusion additionally to brain perfusion equal to pulsatile devices and decreased infection rates. (47,49)

Negative aspects are thrombus formation, the need of large-sized ventricular apical cannulation and size limitation to small patients < 1.5m^2. (47)

About **pneumatic pulsatile pumps:** Besides the Berlin Heart EXCOR® (BerlinHeart, Berlin, Germany) the MEDOS VAD® (Medos Medizintechnik GmbH, Stolberg, Germany) is used in Europe for small children to support left, right and biventricular heart insufficiency. These systems are pulsatile pneumatically driven and paracorporal. The MEDOS VAD® consists of tubes to connect and a pump chamber with a polyurethane trileaflet valve to imitate opening behaviour and flow resistance of the original valve. Connections to the patient's heart are the right atrium and pulmonary artery (right ventricle support) and the left ventricle apex and aorta ascendens (left ventricle support), consequently both, when biventricular support is needed. Similar to other VADs this system can be used for BTT and BTR. Indications are low cardiac output syndrome refractory to medical treatment with beginning multi-organ failure, consequently NYHA (New York Heart Association) VI. Anticoagulation after implantation is done with intravenous Heparin and later switched to oral Coumadin. Most common complications are bleeding and thrombus formation in the valve sinuses leading to pump chamber change. Further complications are infection, neurological events, sepsis, multi-organ failure and technical defects. (50)

Device	Rota-Flow	Levi-tronix	Tandem Heart	Berlin Heart	Thora-tec	Heart MateII	Micro Med de Bakey
Intra/ Para-corpo-ral	Para.	Para.	Para.	Para.	Para.	Intra.	Intra.
Du-ration Of Support	Short-term	Short-term	Short-term	Long-term	Long-term	Long-term	Long-term
Device Type	Rota-tional/ Centrifu gal	Rota-tional/ Centrifu gal	Rota-tional	Pusher plate	Pusher plate	Axial	Axial
Flow Type	Cont.	Cont.	Cont.	Puls.	Puls.	Cont.	Cont.
Power source	Electric	Electro-Mag-netic	Electric	Pneu-matic	Pneu-matic	Electric	Electric
Fill	Vacuum Assisted	Vacuum Assisted	Vacuum assisted	Vacuum assisted	Vacuum assisted	Im-peller's Kinetic energy	Vacuum assisted
Stroke Volume ml				10,25, 30, 50,60, 80	65		
Speed Rpm	0-4500	0-5500	300-7500			6000-15000	7500-12500
l/min	0.5-6	<1.5	<5	Variable	<6	>2.5	1-10
BSA m^2	No mini-mum	<0.5	>1.3	>0.2	>0.7	>1.4	>0.7-<1.5

Table 4 - VADs used for cardiac support in children, adapted from E.B. Mossad et al. (51)

1.3.5 Total artificial heart

The total artificial heart (TAH) completely replaces the original heart. Common types are the CardioWest® Total Artificial Heart (SynCardia Systems, Tucson, Ariz., USA) and the AbioCor® Implantatable Replacement Heart (ABIOMED, Denvers, Mass., USA). The TAH consists of two ventricles including orthopic valves and functions as a pneumatically driven pulsatile device. (52,53)

Morreim et al. reported on the AbioCor study. Included were 15 patients in biventricular heart failure. All patients were ineligible for heart transplantation, on maximal medical support and with a 70% probability of death in the next 30 days. Because of the device's size all patients were male. (54)

Copeland et al. reported on the CardioWest as a BTT in a nonrandomized, prospective study with use of a historical control group. The survival rate to transplantation in the group of patients (81 patients) who received the CardioWest device was 75%, while survival in the control group (35 patients) was 46%. (52)

As a result of complete heart replacement various types of complications occurring with assist devices like valvular regurgitation, cardiac arrhythmics and low blood flow, do not occur. When VADs are contraindicated, in cases of aortic regurgitation, cardiac arrhythmias, ventricle thrombus formation, aortic prosthesis and acquired ventricle septal defects, the TAH is indicated. (52)

The application of TAHs is limited by size; accordingly the device is not available for children and other small patients. Advantages come with the lack of skin penetration (complete implanted) and consequently a lower risk for infection. Disadvantages are thrombus formation, bleeding, infection, device malfunction and neurological events, as in other assist devices. (52,53)

1.4 Berlin Heart Excor

The Berlin Heart Excor ® (Berlin Heart AG, Berlin, Germany) is a mechanically driven pulsatile assist device for children with terminal heart failure. The BVAD is used for short to long-term support (e.g. as bridge to transplantation (BTT), bridge to recovery (BTR) or destination therapy (DT)).

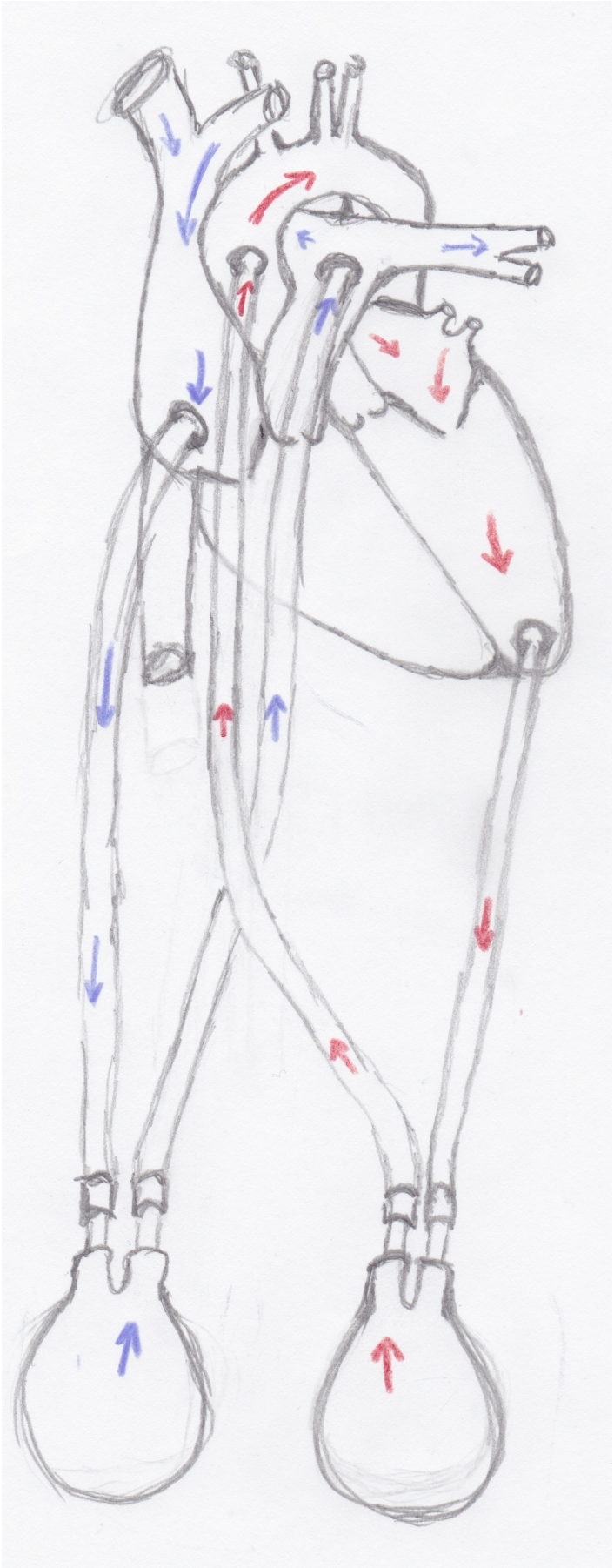

Figure 1 - Schematic illustration of the Berlin Heart Excor

1.4.1 About the device

The Berlin Heart Excor® (Berlin Heart AG, Berlin, Germany) is a paracorporal pneumatically pulsatile driven mechanical assist device for children with terminal heart failure. (55) In 1990 the first Berlin Heart Excor, in adult-size 50-ml pump, was implanted in a nine years-old child for one week with an uneventful postoperative time after heart transplantation. (41)

The blood pumps are pneumatic compressor-operated diaphragm pumps with trileaflet polyurethane valves for children sizes: 10-ml, 25-ml, 30-ml pumps; and tilting disc valves (Sorin Biomedical, Torino, Italy) or trileaflet polyurethane valves for adult pump sizes: 50-ml, 60-ml, 80 ml. The pumping house is made of translucent, semirigid polyurethane and is divided into two parts, a blood and air chamber, by a flexible three-layered diaphragm. Driving layers are the air chambers facing two layers; the blood-facing layer is moved passively. All blood-touching surfaces are heparin coated by the Carmeda process (Carmeda, Upplands Väsby, Sweden) and have been described as effective for six months, although supporting time has been reported over two years. Out-and inflow-connectors are made of polished titanium, appropriately matching the silicone cannulas. The cannula's outer surface is smooth Dacron (C.R. Bard, Haverhill, Pennsylvania) coated to provide tissue ingrowth and hence minimize driveline infections. The cannulas are designed in different dimension, for adults, with an inside diameter of 12mm, for paediatric patients, with inside diameters of 4.8, 6 and 9mm, suitable for different sizes and anatomy. For adults connecting cages of the atrium cannulas are available in lengths from 22mm to 26mm, for children the connecting cages are standardized. There are also different sizes for left apex insertion. The sewing ring at the insertion point is Dacron (Impra, subsidiary of L.R. Bard, Tempe, Arizona) covered. The arterial cannulas for small devices have a short titanium reinforced toe, called "press button" tip, for adequate arterial insertion. As an effect of these cannulas contrary to the cannulas of a heart-lung machine, the heart's afterload is reduced. The Berlin Heart Excor ® is driven by the IKUS driving unit, which is composed of three separate compressor units, one for each pump and one back-up compressor. If one or both other compressors malfunction, the back-up compressor steps in automatically with 90 beats per minute. Two redundant internal computers with a back-up battery, (lasting up to one hour) to enable the device to run in case of power failure, control the system. The pump's operating mode is adjusted for uni- or biventricular support. Adjustable parameters are pump rate between 30 to 150 beats per minute, systolic pump

pressure up to 350mmHg, and diastolic pump pressure up to -100mmHg and relative systolic duration length revising 20% to 70%. Comparatively high systolic pressure is needed in children because of the high flow resistance of the paediatric cannulas. In biventricular mode the device can be switched between synchronous for simultaneous, asynchronous for alternating and separated for independent pump function. Especially for right ventricle recovery on BVAD support, the independently controlled mode is used to reduce the right ventricle's output to prevent pulmonary oedema. (55)

1.4.2 Indications/Limitations

Decisive factors determining the therapeutic success are device selection and right timing of VAD implantation, which means, before cardiogenic shock with multi-organ failure occurs. (51)

To specify, VAD support is indicated if weaning from cardio-pulmonary bypass (CPB) fails or poor ventricle function is revealed by echocardiography combined with a cardiac index below 2, mixed venous saturation below 40%, oliguria, metabolic acidosis and insufficient peripheral perfusion despite combined treatment with catecholamines, phosphodiesterase inhibitors, bicarbonates, diuretics, afterload reduction and mechanical ventilation. Stiller et al. reported that sufficient unloading of the left ventricle is reached by outflow cannulation done by apex cannulation, leading to reduced left ventricle enddiastolic pressure, resulting in immediate afterload reduction of the right ventricle by 15-25mmHg. Hence first the LVAD is implanted followed by optimization of medical right heart treatment with nitric oxide, iloprost, oxygen and a low dose of catecholamines. Subsequently right heart function is assessed and in case of right heart insufficiency the RVAD is implanted. This procedure often leads to LVAD support only, lowering the long-term complications rate, which is associated with BVAD support. (56)

There are only a few relative contraindications for VAD treatment. Widely accepted contraindications for VAD support are malignant neoplastic disease with a very limited life expectancy, advanced multi-organ failure, complex congenital heart lesions involving intra-cardiac shunts or irreversible pulmonary failure and severe extra-cardiac malformations such as chromosomal or genetic syndromes with poor quality of life prognosis. There is evidence that similar to adults, earlier VAD implantation results in better outcome, especially in children under one year of age. (35) Nevertheless each patient must be viewed separately. (49) The availability of VAD for support in children with a

very low birth weight is limited, but the Berlin Heart Excor device is applicable to a body weight as low as 3kg.

1.4.3 Implantation/Operation (6)

Adequate preparation includes preoperative transoesophageal echocardiography (TEE) to rule out intracardiac shunts, (e.g.residual ventricle defects, patent foramen ovale) reveal the presence of any thrombus formation and show semilunar valve function. Further diagnostics are not needed because most of the patients planned for BVAD are HTx patients and therefore evaluated.

The surrounding lines of the surgical area are from the pubis to the neck and from the right mid-axillary line to the left mid-axillary line. For this area skin disinfection and draping have to be done. Cannula skin exit points should be marked on the skin and should be two cm from the costal margin because of the Dacron cuff. Furthermore "VAD in lap syndrome" should be avoided and therefore the surgeon has to consider the sizes of pump and cannula when performing skin incision.

The following step is sterno-or re-sternotomy due to the patient's history. As much dissection as possible should be done before starting heparinization and cardiopulmonary bypass. Skin exits for cannulas should be done carefully preventing any injury of the peritoneum. Insertion points for cardiopulmonary bypass cannulas should be: the most distal extent possible for arterial cannula and bicaval for venous cannula. During the BVAD implantation the heart is under cardioplegic arrest.

At this point the heart has to be mobilized for implantation of the LVAD inflow cannula in the left ventricular apex (core incision, left ventricle inspection, series of horizontal mattress sutures, sutures tied). Finally the cannula is brought through the previously made skin tunnel. The LVAD outflow cannula is first brought through the skin tunnel and then placed in the lateral tract of the ascending aorta through longitudinal incision made before. The smaller cannulas are inserted with two concentric purse-string sutures, the larger cannulas are simple anastomosed.

The RVAD outflow cannula is carefully inserted into the main pulmonary artery, like the aortic cannula, avoiding distortion of the pulmonary valve. The RVAD inflow cannula is inserted like the small LVAD inflow cannula into the right atrium of the heart.

Now the cannulas are attached to the blood pumps and the de-airing system is started. Until the de-airing process is confirmed by TEE and meticulous inspection of the pump

chambers, the cannulas remain clamped. After this process BVAD is started and the patient is separated from the cardiopulmonary bypass and weaning is started. The de-airing needles are left in the pump chambers until the pumping system is working sufficiently without any air bubbles left in the cambers. As hemostasis is satisfactory and PTFE membranes are positioned (around the ventricular apex, between aorta and pulmonary artery, lateral to the right atrium, anterior to the innominate vein and to the VAD cannulae) the chest is closed. If hemostasis isn't satisfactory (in case of prolonged surgery) the chest has to be left open and closed after a few days when hemostasis is reached.

1.4.4 Weaning and explantation

In case of signs of myocardial recovery an attempt can be made to wean the patient from the Berlin Heart Excor. First ß-blockers and ACE-inhibitors are administered and the pump rate is slowed down. Then the native hearts function is assessed by echocardiography. The next step is to check the aPTT (activated partial thromboplastin time) and give a heparin bolus (50-100 IU/kg) previous to stopping the device for 5 to 15 minutes. During the whole weaning attempt the heart's function is supervised by echocardiography. During this time ejection fraction should be over 50% and the left ventricular end-diastolic diameter (LVEDD) should be age related and $<95^{th}$ percentile. The pump should be moved by hand twice every 30 seconds to prevent clotting. If the weaning attempt is successfully, the device is explanted using cardio-pulmonary-bypass. (57)

If the Patient has reached transplantatbility, this means satisfactory organ recovery, no severe neurological deficit, desirably extubated and is without infection, heart transplantation can be performed. Immunosuppressive therapy consists of triple immunosuppressive regime. A possible rejection reaction is revealed by intramyocardial electrogram and myocardial biopsy. (42)

1.4.5 Anticoagulation

Perioperative anticoagulation management around Berlin Heart implantation is comprised as follows. The first step in the perioperative period is to stop the use of anti-aggregation (acetysalicyl acid, clopidogrel) and anti-adhesion (dipyrimidol) drugs; instead heparin is used as anticoagulation drug, depending on clinical data of the patient. Interoperatively heparin is used for extracorporal circulation, depending on the Hepcon test (Medtronic). At

the end of surgery protramine is given to achieve normal activated clotting time (ACT). No anticoagulation drug is used in the first eight postoperative hours. Thereafter, if no bleeding occurs, heparin is administered again. If platelet function and platelet count are normal, anti-aggregation (acatylsalicyl acid) and anti-adhesion (dipyrimidol) drugs are used. When the patient starts eating, anti-vitamin (coumadin) is given too. The dosage for anticoagulation with heparin (3-20 IU/kg/h) and coumadin (0.1-1.5 mg/kg/d) is depending on thrombelastography, activated partial thromboplastin time 50-100 seconds and international normalized ratio (INR) 3.0-3.5. Anti-aggregation with acetylsalicyl acid (0.5-5 mg/kg/d, max. 300 mg/d) is administered in dependency of platelet aggregation test (ARA). And anti-adhesion with dipyrimidol (2-15 mg/kg/d, max. 1200 mg/d) is given, depending on beta-thromboglobuline (ß-TG), platelet factor 4 (PF4) and platelet count. (38) Antithrombin III (AT III) is measured and substituted when it is below 70%. (57)
Schmitz et al. reported about a 15-year-old male patient who developed heparin-induced thrombocytopenia type II (HIT II) after six weeks of heparin administration after implantation of a Berlin Heart Excor LVAD. Instead he was treated with argotroban and in his further course he successfully underwent heart transplantation after 65 days on support. (58)

1.4.6 ICU management

Contrarily to LVADs, where right ventricular function has to be particularly monitored and if needed supportive right ventricular medical treatment has to be started (inhalative NO, inotropic support). This is of less importance when a BVAD is implanted. Normally after implantation of the Berlin Heart Excor no or severely less (to maintain adequate main arterial pressure) inotropic support is needed. If blood pressure is too low, complete filling and emptying of the blood chamber should be checked. Different causes that influence the blood pressure need to be checked (like the device itself, hemodynamic values). First the interval of systole, diastole and the pump rate need to be reviewed. Second, influence by volume changes like administering infusions or diuretics have to be overviewed. Third, the administration of noradrenalin (arterenol) in case of peripheral resistance loss or sepsis has to be checked. (57)
To ensure good protection of the myocardium and potential recovery of the myocytes, in case of BTR, the afterload is reduced with milrinone or ACE-inhibitors and ß-blockers. (56)

To prevent the patients from exceeding red cell transfusion, oral ferritin and subcutaneous erythropoietin is given to children with up to 20 kg body weight. Enteral nutrition is administered a few hours after operation. (57)

In the first week after implantation second-generation cephalosporines are used preventively and vancomycin is administered if the chest remains open. After this period antibiotics are used if infection is suspected or proved. The patient should be extubated and mobilized as early as possible. Daily pump inspection is particularly important to search for clots, especially in the area of the valves according to Berlin Heart's protocol. If no bleeding or secretion occurs, a specially trained nurse performs dressing changes twice a week. (42,57)

2 Material and methods

2.1 Aim of the study

This report describes the pediatric experience with the paracorporeal biventricular assist device, Berlin Heart Excor, used at the Medical University Graz, Austria. We investigate our experience with the BVAD Excor focusing on adverse events in patients below 18 years. Death on device, survival to transplant and after transplantation, neurologic events (TIA, insult, bleeding), bleeding events other than cerebral, renal failure, laboratory values (relevant for anticoagilation and hemolysis) will be reviewed by single chart analyses retrospectively.

The question is of importance because; contrary to adult patients where a lot of different devices are available, for small children needing BVAD support only the Berlin Heart Excor device is available.

The research question is relevant for children because of lack of alternative assist devices.

2.2 Collective of patients

Between 2006 and 2012 nine patients (age range: 6 to 67 years) underwent BVAD Excor implantation at the Medical University Graz, Department for Transplantationsurgery, Graz, Austria. All patients were suffering from end-stage heart failure requiring positive inotropic support without any possibility of weaning from i.v. catecholamines. Subject of this study were patients aged below 19 years with end-stage heart failure treated with BVAD Excor implantation (n:4). These four patients were all male, aged six, thirteen, fourteen and sixteen years at time of VAD Excor implantation. Diagnoses leading to end-stage heart failure requiring BVAD Excor support were: postcardiotomy failure (n:1), dilatative cardiomyopathy (n:2) and heart failure of unknown origin (n:1).

The study protocol was submitted to the Ethics committee at the Medical University of Graz. On the 20th of April 2012 the ethics committee approved the study. The vote is appended to the manual.

After approval demographic and clinical data were collected retrospectively from medical records. This study explored overall survival, waiting time for heart transplantation (HTx), complication profile on the BVAD Excor support and cause of death in two patients. Determined laboratory parameters were International Normalized Ratio (INR), hemoglobin (hb), hematokrit (hkt), creatinin (crea), bilirubin (bili), serum pro brain natriuretic peptide (s-p-P) and lactatdehydrogenasis (LDH). Determined ultrasound scan parameters were central venous pressure (cvp), mean arterial pressure (map), tricuspidal insufficiency (tci), left ventricular enddiastolic diameter (LVEDD) and ejection fraction (EF). Laboratory parameters as well as ultrasound scan parameters were evaluated preoperatively, during BVAD Excor support time (1,2,3,6,9,12,18 months after BVAD Excor implantation) and after HTx (1,2,3,6,9,12,18 months after transplantation). The laboratory parameters leucocyte count and platelate count were overviewed before BVAD Excor implantation and during BVAD support (1,3,6,12, 18 months after BVAD Excor implantation). Complication profile included neurological events (defined as transischemic attack, prolonged neurologic deficit, insult or cerebral bleeding), bleeding needing surgical revision or blood transfusion, pump chamber exchange due to thrombosis or other malfunction, renal failure defined as need for hemodialyses and severe hemolyses needing blood transfusion.

2.3 Collection of data and statistical analysis

To ensure high quality output data were collected from all available patient files and electronic medical records at the department for pediatric cardiology, heart surgery and transplantation at the Medical University of Graz. Between April and August 2012 data collection was performed. Patient data was anonymized and treated as strictly confidential; there were no personal interviews. Results are based on documentation of the department for pediatric cardiology, heart surgery and transplantation at the Medical University of Graz.

The data obtained was entered in a protocol Excel spreadsheet and further statistical analyses were performed using SPSS software (version 15.0; SPSS Inc, Chicago, IL). Data is given as descriptive statistics as mean values ± standard deviation (SD).

3 Results

3.1 Description of the patients

Patient number 1 (#1). A six-year-old male patient (115 cm length, 16,42 kg weight) without known relevant previous medical history was admitted to hospital because of recurring coughing accompanied by vomiting, moreover he was tired and exhausted. Infectious screening was started (blood cultures, image diagnostics) but no infectious origin was found; viral myocarditis and metabolic disease as a cause of heart failure were ruled out by diagnostics. The thorax X-ray showed signs of cardiomegaly, further in the ultrasound scan dilation and impaired contractility of both ventricles was visible. The diagnosis of dilated cardiomyopathy (DCM) was suspected. The child's clinical presentation deteriorated and inotropic support had to be started. Despite maximum inotropic drug therapy (Dobutrex 12 µg/kg/min, Suprarenin 0,075 µg/kg/min, Arterenol 0,1 µg/kg/min, Protrop 0,5 µg/kg/min) multi-organ failure developed and decision was made to implant a mechanical assist device. Accordingly a BVAD (Berlin Heart Excor) was implanted using the heart lung machine. The operative course was uneventful; placements for the Excor cannulae were: apex of the left ventricle and ascending part of the aorta (for the left side support) and right atrium and pulmonary artery (for the right side support). Cannula positions were verified by intraoperative esophageal echocardiography. The operatively performed biopsy revealed DCM; viral myocarditis was once again excluded as diagnosis. Systemic inflammatory response syndrome and bilateral pleural effusions complicated the immediate postoperative course. Pleural effusions were treated by drainages (no severe bleeding occurred). Hemodynamic parameters stabilized quickly and weaning of inotropic support was done as well as extubation. Recovery after the operation was satisfactory; unloading of both ventricles with the Excor was sufficient as well as the filling of both pump chambers. Primary anticoagulation with unfractionated Heparin, Aspirin and Persantin was switched to oral anticoagulation with Sintrom. No relevant hemolysis occurred.

In the further course the contractility of both ventricles improved. For this reason repeated weaning attempts from the Excor were done according to the protocol from the German Heart Institute Berlin. (59) Unfortunately weaning criteria were not met and all attempts

failed. The patient was listed as high urgent status for heart transplantation (HTx) after two months on BVAD support.

Recurring epistaxis was seen as complication on mechanical support, but no other severe bleeding complications occurred. Pump chamber exchange on the right side was needed twice, once due to thrombus formation (109 days after BVAD placement) and the other one due to rupture of the surface membrane (298 days after BVAD placement). In addition pump head exchange on the left side was needed once because of damage due to mechanical fatigue. Further complications included changing of the tubing system four times, three times on the right side and one time on the left side. Reasons were damage to the tubing system due to mechanical fatigue.

At the exit sites of the cannulae Caro luxurians and peri-wound macerations were noticed. Consequently recurring drive-line infections occurred, treated successfully with intravenous antibiotics. One year after BVAD implantation recurring vomiting with problems in nutrition occurred, finally leading to nutrition by nasogastric tube for seven months.

The patient hospitalized for the entire BVAD support time. He suffered from psychological stress, which led to panic attacks after 525 days on support. These problems were treated with psychotropic drugs and family support.

After 545 days of BVAD support, a suitable donor organ was available and HTx took place successfully. Panel reactive antibodies were negative. Waiting time on HU (high-urgent) waiting list was 480 days; overall there were four heart-offers; our institution due to medical reasons rejected three. The HTx was hindered by adhesions and prior anticoagulation therapy. Immune suppressive therapy was started with Antithymozytenglobulin, Mycophenolat-Mofetil, Methylprednisolon and Cyclosporin A, and was then switched to Tacrolismus and Prednisolon. Twelve days after HTx the first myocardial biopsy control showed no cellular rejection. Echocardiographic controls revealed no further signs of rejection episodes.

Despite antiviral prophylaxes a reactivation of EBV-infection (Epstein-Barr virus infection) occurred. During antiviral treatment temporary renal failure occurred and improved after readjustment of the dosage of the antiviral therapy.

Three weeks after transplantation thrombosis of the vena cava superior developed and reoperation had to be scheduled. The thrombus was successfully removed mechanically.

The patient is currently at home and scheduled for routine follow-up visits every four weeks at our institution.

Patient number 2 (#2). A 13 years old male patient (160 cm height, 50 kg weight) was transferred from another hospital within Austria with an already implanted BVAD (Berlin Heart Excor) to our institution. The cardiac background history of the patient was a congenital aortic valve insufficiency grade IV that was corrected by a ROSS-Operation (autograft: replacement of the insufficient aortic valve with the native pulmonary valve; homograft: replacement of the pulmonary valve with a donor pulmonary valve (60)) at the age of nine. At the age of 14, aortic root dilatation occurred and surgical repair was attempted. It was decided to perform a Yacoub-Operation in which the sinus aortae are replaced with a crown-like tailored Dacron-velour-prosthesis, without causing functional disturbance between the aortic root and the aortic valve leaflet. (61) Intraoperative weaning from cardiopulmonary bypass was not possible and biventricular heart failure occurred. Implantation of an intra-aortic balloon pump did not improve the situation and consequently an arterial-venous ECMO was implanted. During the following two days on ECMO support an increased tendency of bleeding was noticed. Further no signs of myocardial recovery were detected. Excor BVAD implantation was performed without severe intraoperative complications and ECMO system was explanted. Placements for the Excor cannulas were: apex of the left ventricle and ascending part of the aorta (for the left side support) and right atrium and pulmonary artery (for the right side support). Finally the patient was transferred to our institution for further treatment. Additionally secondary closure of the sternum was needed because of bleeding. The immediate postoperative complications were similar to the first patient (see above) including a systemic inflammatory response syndrome and bilateral pleural effusions.

Hemodynamic parameters stabilised quickly and weaning of inotropic support was done as well as extubation. Recovery after the operation was satisfactory, unloading of both ventricles with the Excor was sufficient as well as the filling of both pump chambers.

Undergoing maximum drug therapy (ACE-Inhibitors, beta-blockers, diuretics) heart function improved, left ventricle ejection fraction enhanced, but criteria for weaning attempts from the BVAD couldn't be reached, consequently the patient was listed for HTx.

Primary anticoagulation with unfractionated Heparin, Aspirin and Persantin was switched to oral anticoagulation with Sintrom in the further course. Recurring deposits of fibrin in the right chamber occurred and were well treated with unfractionated Heparin. Pump chamber exchange on the right side was needed due to thrombus formation after 186 days on BVAD support. Up to recurring epistaxis there were no further bleeding complications.

Driveline infections occurred, first after 185 days on BVAD support and reoccurring after 242 days on BVAD support. These were treated successfully with intravenous antibiotics.
The whole time in the intensive care unit was characterized by mood swings accompanied by anxiety and despair, depression, auto-aggression and aggression against others. Therefore feeding problems occurred in the initial period of BVAD support.
After 262 days on BVAD support the patient underwent heart transplantation (HTx) successfully, after 20 days on HU waiting list. The HTx was hindered by adhesions and prior anticoagulation therapy. Immune suppressive therapy was started with Antithymozytenglobulin, Mycophenolat-Mofetil, Methylprednisolon and Cyclosporin A. and was later switched to Tacrolismus and Prednisolon. Before HTx plasmapheresis was performed to eliminate pre-formed irregular HLA-antibodies. The time after HTx was complicated by antiviral treatment because of CMV (cytomegalovirus) positive donor organ and CMV negative recipient.
26 days after HTx the myocardial biopsy revealed a rejection reaction grade II, requiring treatment. The myocardial biopsy control revealed marked improvement, rejection reaction grade I.
One year after HTx the patient was admitted to hospital because of abdominal pain, which was McBurney-positive. A tumorous mass was removed without any reference to pathology. Moreover recurring abdominal complaints of unknown origin had been a burden before and after the abdominal operation for the whole year. Finally the treatment diagnosis was hemorrhagic colitis.
To our knowledge the patient was discharged from hospital in good general health.

Patient number 3 (#3). A 16 years old male patient was admitted to hospital due to deterioration of his general condition accompanied by upper abdominal pain. This was the first time the patient was diagnosed with DCM. At admission the ultrasound scan of the heart showed a depressed left and right ventricular function, high-grade mitral regurgitation and liver enlarged and deferred six fingers below the right costal arch. Heart failure therapy was intensified but the heart function deteriorated and inotropic support had to be started for stabilization. For diagnostic reason endomyocardial heart biopsy was taken to rule out active myocarditis. HTx appeared to be the only suitable option and as all necessary diagnostic evaluation was done the patient was listed at Eurotransplant for heart transplantation. As he fulfilled the high urgent criteria, the patient was listed high urgent. Further biventricular deterioration led to signs of multi organ failure despite maximum

inotropic support and therefore as bridge to transplantation BVAD (Berlin Heart Excor) implantation was indicated. The operation was carried out without major complications and standard placements for the VAD cannulae were done. Placements for the Excor cannulae were: apex of the left ventricle and ascending part of the aorta (for the left side support) and right atrium and pulmonary artery (for the right side support). The patient was brought to the Intensive Care Unit (ICU) for further treatment. Anticoagulation was done according to the institutional standard protocol. Minor postoperative complications included hematoma in the anterior mediastinum treated conservatively and a pneumothorax treated by drainage. The patient recovered well after the operation. Two weeks after the operation pericardial effusion, pleural effusion on the left side and post pulmonary infarction pneumonia, accompanied by fever were noticed and led to sepsis and acute respiratory distress syndrome (ARDS) requiring ventilation. At that time the patient was already on oral anticoagulation with Marcumar and the target INR was 2.5 to 3.5. Despite sufficient anticoagulation multiple septic thromboembolic events to spleen and kidney occurred. Anticoagulation was hard to adjust due to infection but finally the patient recovered, was extubated and mobilization was possible. Six weeks later the patient once again showed an episode of pneumonia with fever and pleural effusions treated successfully with antibiotics and thoracic drainage.

At the ward he developed clinical symptoms of right heart failure (ascites) treated by adaption of the right ventricle's pump.

Bleeding complications noticed as epistaxis were reported frequently during the whole BVAD support time. Two episodes of tachycardia (first two weeks after BVAD, second five weeks after BVAD implantation) were treated conservatively. After 11 weeks on BVAD support a fibrin thrombus was noticed in the right pump chamber of the BVAD, but disappeared under intensified anticoagulation. Furthermore the patient developed ascites.

Not surprisingly the patient had mental health problems with one acute episode during his stay in the Intensive Care Unit.

After 84 days on BVAD support our patient showed slurred speech and hemiparesis on the left side. CT scan of the brain was planned but not conducted because of deterioration of the patient's condition with bilateral wide and fixed pupils. Anticoagulation at this time was PTT: 72 seconds, Quick: 28% according to INR: 2.8. Further medical intervention was ruled out due to the patients deteriorating state. The patient died after 84 days on BVAD support.

Patient number 4 (#4). A 14 years old boy (160 cm height, 40 kg weight) was under medical supervision because of recurrent syncopes of unknown origin. He had already had five syncopes that occurred during sport and after jumps into cold water. The syncopes were accompanied by weakness and dizziness but without palpitations. At the day of admission the patient had a syncope lasting for four minutes during physical education class. At the time of arrival of the emergency physician the patient was already conscious in stable hemodynamic conditions. During transfer to the department of children cardiology at the Medical University Graz the hemodynamic situation worsened and he was spitting foaming blood. At the time of admission in the emergency room sufficient cardiopulmonary resuscitation had to be performed for a few minutes. Peripheral venous-arterial ECMO implantation was done and a stabilization of hemodynamic parameters achieved. Echocardiography revealed biventricular heart failure with significant reduction of ejection fraction. Myocarditis was the initially suspected diagnoses. After initial stabilization under ECMO therapy mitral valve insufficiency occurred and led to oedema and ventilation problems. It was decided to surgically implant a left arterial VENT catheter (catheter which recompresses the atrium by suction).

The tentative diagnosis of myocarditis could be verified, neither by endomyocardial biopsy nor by image diagnostics, blood cultures or other diagnostic tools; instead DCMP was adopted as the diagnosis to deal with.

Subsequently, after the VENT application, the patient's condition slightly improved, but no signs of myocardial recovery could be seen. Echocardiography revealed hypo- or akinesia of posterior, lateral and inferior heart wall. Consequently a BVAD was implanted. The intraoperative course was complicated by massive bleeding; because of severe bleeding the sternum was left open. Hemodynamic stabilization was achieved but numerous blood products had to be given, leading to acute lung injury. Because of impossibility to oxygenate the patient, additionally to the BVAD a venous-venous ECMO had to be established. Suspension of bleeding couldn't be achieved. Bleeding occurred not only from the surgical field, but also endotracheal subsequently leading to suction of the tube. An overall of five-resternotomies had to be done in the following four days, a surgical cause of bleeding could not be found though. Besides recurring blood transfusions, fresh frozen plasma, platelet transfusion, clotting factors and desmopressin administered; heparin was completely antagonized and stopped. Finally as inotropic support was maximized and no hemostasis was reached, the patient died due to massive bleeding and multi-organ failure.

Autopsy findings revealed an angiodysplasia of the small coronary blood vessels. Further findings were mucoide degeneration of the aorta, multiple ischemic infarctions of the heart of different ages, liver infarction, signs of beginning pulmonary hypertension and ischemic changes in the brain.

3.2 BVAD settings

Patient	Frequency Beats/minute	Systole mmHg		Diastole mmHg	
		Left side	Right side	Left side	Right side
Pat1	80	240	155	-45	-35
Pat2	70	200	150	-40	-25
Pat3	64	210	130	-25	-20
Pat4	70	230	140	-30	-20

Table 5 - BVAD settings

3.3 Anticoagulation

Anticoagulation was started postoperative with heparin intravenous when no severe bleeding occurred with a target aPTT of 60 to 80 seconds. Acetylsalicylacid (0,5mg/kg/day) was administered as soon as all drains were removed. Dipyridamol was used (3x75mg/day) and Coumadin was administered at the ward with a target INR of 3.0 to 3.5 (starting dose: 0.2mg/kg/day, single dose). To achieve balance between minimizing thrombembolic events and bleeding complications, the thrombocyte aggragation test (TAT) and thrombelastography (TEG) was done to monitor antiplatelet therapy.

3.4 Preoperative values

Diagnosis in these four patients were: postcardiotomy heart failure (n:1), dilatative cardiomyopathy (n:2) and terminal heart failure of unknown origin (n:1). As shown in the table below, all patients were in a severe heart condition, Intermac Level 1 and 2, and under inotropic support before BVAD implantation. Left ventricular ejection fraction in no patient was higher than 25% and left ventricular enddiastolic diameter was between 41 and 73 mm.

		Pat1	**Pat 2**	**Pat 3**	**Pat 4**
Age	ys.	6.5	13.5	16.5	14
Gender	male/female	male	male	male	male
Year of Implant		2010	2009	2006	2012
BMI	kg/m^2	12.4	19.5	20.3	15.6
Intermacs Level	(1-7)	1	1	2	2
mean BP	mmHg	60	55	80	60
Creatinine	mg/dl	0.6	1	1.7	0.72
Bilirubin	mg/dl	0.82	1.2	1.06	2.39
hb	g/dl	12.5	11.1	12.1	10.9
cvp	mmHg	9	16	20	15
LVEF	%	20	15	25	25
LVEDD	mm	44	55	73	41
TI	Grade	2	1	2	0
Inotropic support		yes	yes	yes	yes
ECMOsupport (days)			2		7

Table 6 - Preoperative values

3.5 Outcomes and complications during BVAD support

Our results are presented in detail below; the summary at the end of this chapter shows an overview of the defined complications.

30 days mortality was 25% (n:1); this patient died on postoperative day four due to massive hemorrhage and multi-organ failure. Patient #3 died on postoperative day 84 due to cerebral bleeding. Mean support time was 223,75 days (4d, 84, 262d, 545d). Two children were successfully transplanted after 262 and 545 days on BVAD support.

Neurological complications occurred in one patient. As before mentioned, patient #3 died due to cerebral hemorrhage after 84 days on BVAD support. At that time INR was 2.8 and PTT was 72 seconds. Besides oral anticoagulation the patient's medical therapy included aspirin 100mg and persantin 75mg three times a day. In the other patients no transischemic attack, prolonged neurological deficit or insult were noticed. The cerebral autopsy of patient #4 did not show a sign of bleeding or insult.

Severe bleeding complications needing blood transfusions were seen in one patient #4. The intraoperative course of patient #4 was complicated by massive bleeding resulting in massive blood transfusions leading to overall five resternotomies in four days after BVAD implantation. No surgical bleeding site could be identified. Additionally peripheral venous-venous ECMO implantation had to be done due to pulmonary failure. The patient died on postoperative day four due to massive bleeding and multi-organ failure. Three patients (#1, #2, #3) frequently reported epistaxis, but all episodes were treated conservatively. No gastrointestinal bleeding or other bleeding complications were noticed during long-term support. Mean INR values for the support time on BVAD can be seen in Figure 2. No severe hemolysis measured by platelet count (PLTs) and LDH needing blood transfusions occurred in patients 1 to 3. PLTs and LDH course can be seen in Figure 3 and 4.

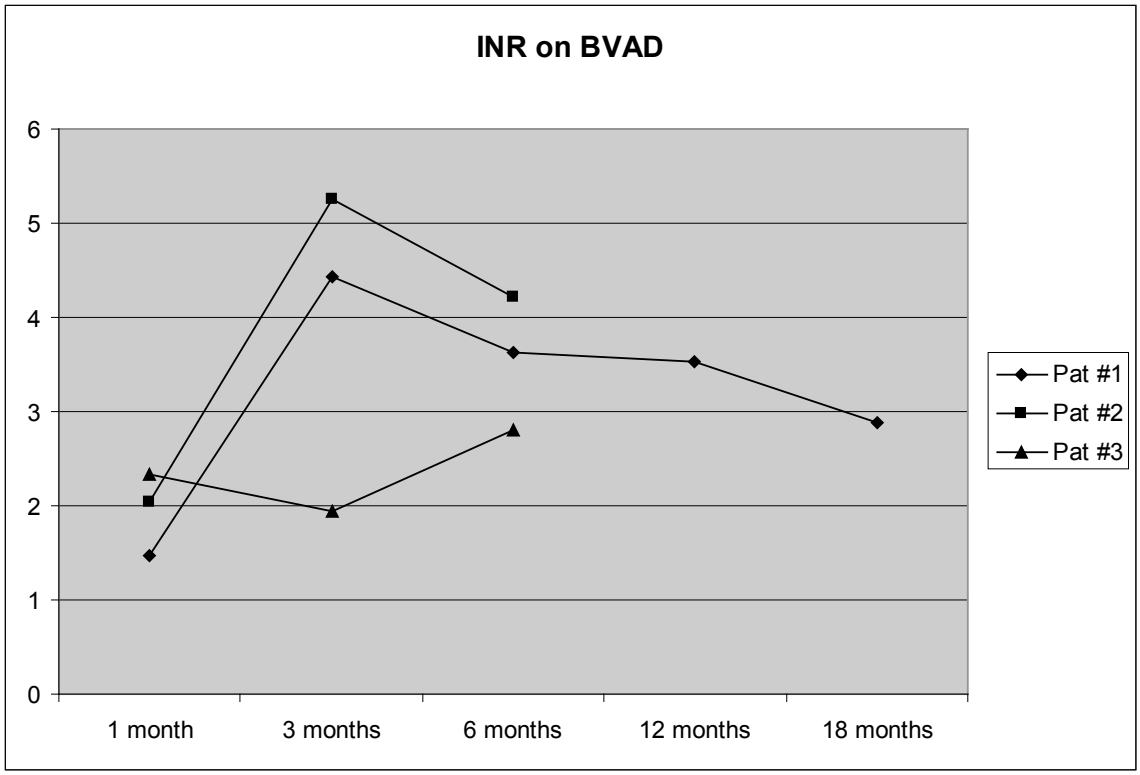

Figure 2 - Mean INR for the support time on BVAD for patient #1 to #3

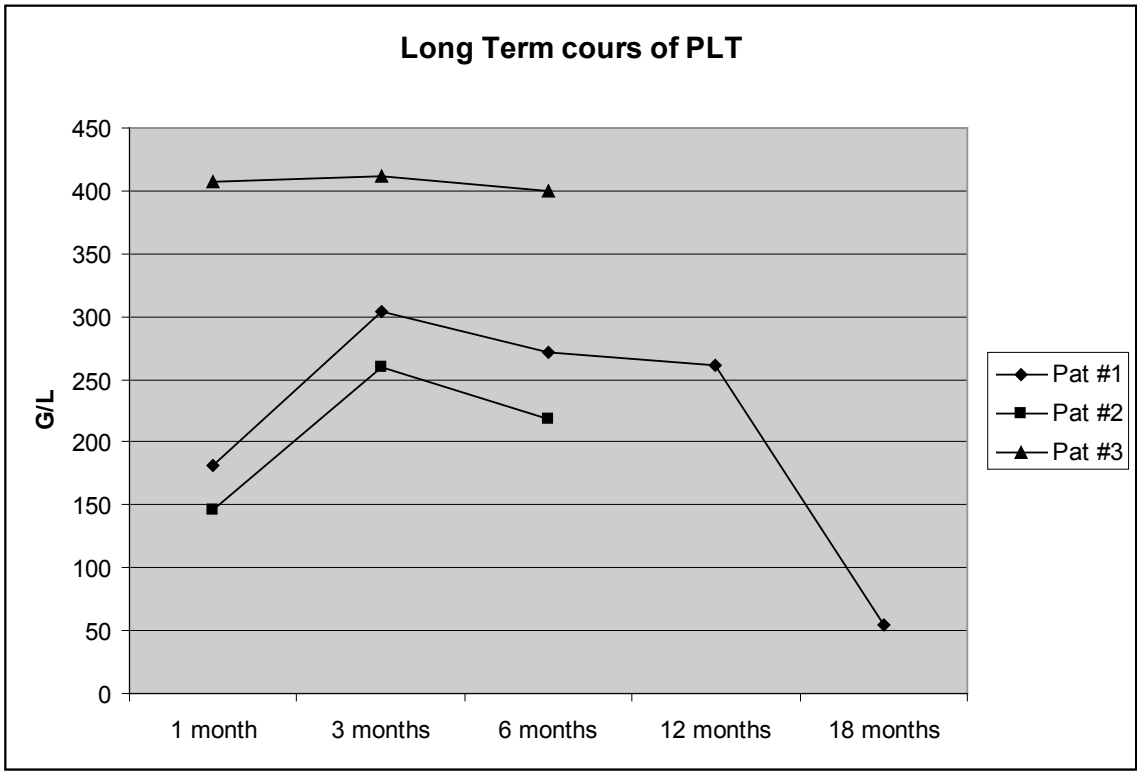

Figure 3 - Course of platelet count (PLT) in G/l for patient #1 to #3

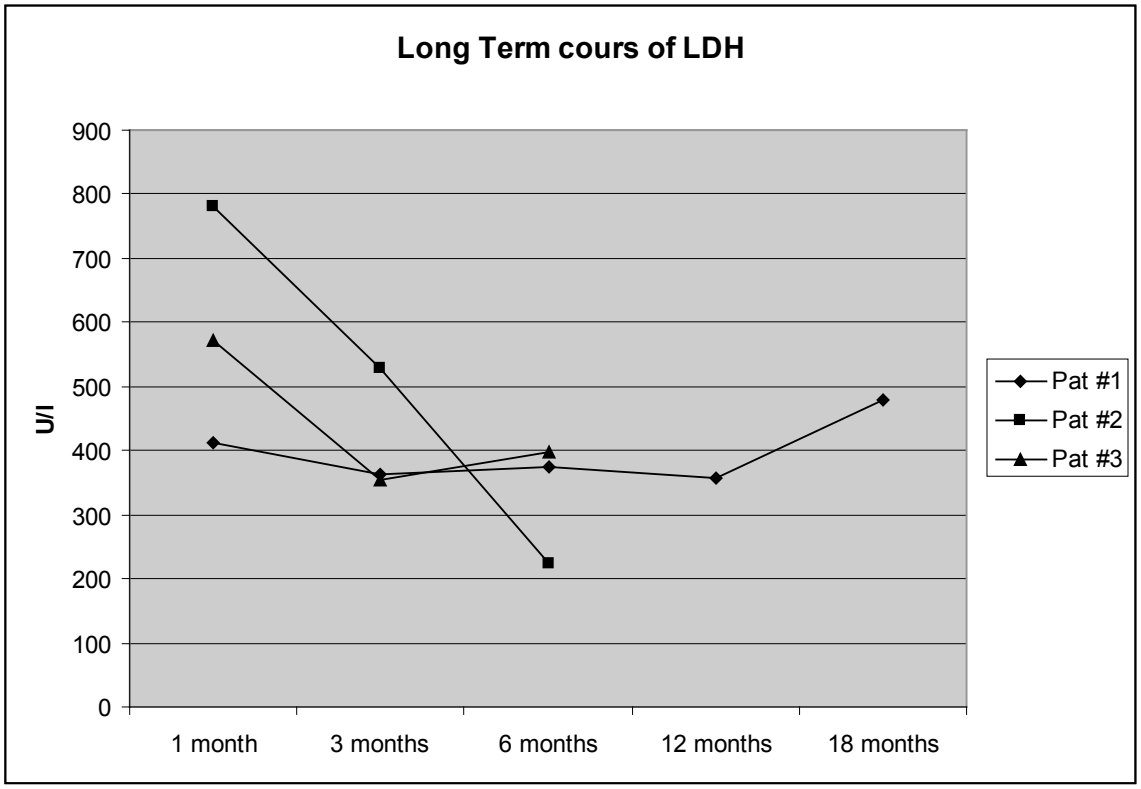

Figure 4 - Course of lactate dehydrogenais (LDH) in U/l for patient #1 to #3

Infection complications occurred in three patients. Drive-line infections were noticed in two patients (#1, #2) with a support time of over six months. The drive-line infections were treated by intravenous antibiotics and local treatment; the first episodes were seen after seven (#1) and nine (#2) months on BVAD support. At the time of drive-line infection elevated C-reactive protein was the only systemic infection signs found. The drive-line infections were recurrent in both patients until HTx. Patient #3 presented with two sever infection episodes, one leading to sepsis (postoperative day 16) with septic emboli in spleen and right kidney and acute respiratory distress syndrome needing re-intubation and ventilation.

Complications associated to the BVAD system: Pump chamber exchange was necessary three times in two patients (#1, #2) due to pump chamber thrombosis (n:2) and partial pump chamber membrane rupture (n:1). After 109 days on support detection of thrombus formation in the left pump led to pump exchange (#1); in the same patient after 298 days partial membrane rupture on the right side pump led to pump exchange. In patient #2 thrombus formation was noticed on the right pump after 165 days on support and finally led to pump exchange after 185 days. In patient #3 thrombus formation was detected on the right side pump but treated conservatively.

As to other complications, in patient #4 postoperative renal failure needing hemodialysis occurred. All other three patients had normal creatinine values in the follow-ups, seen in Figure 5.

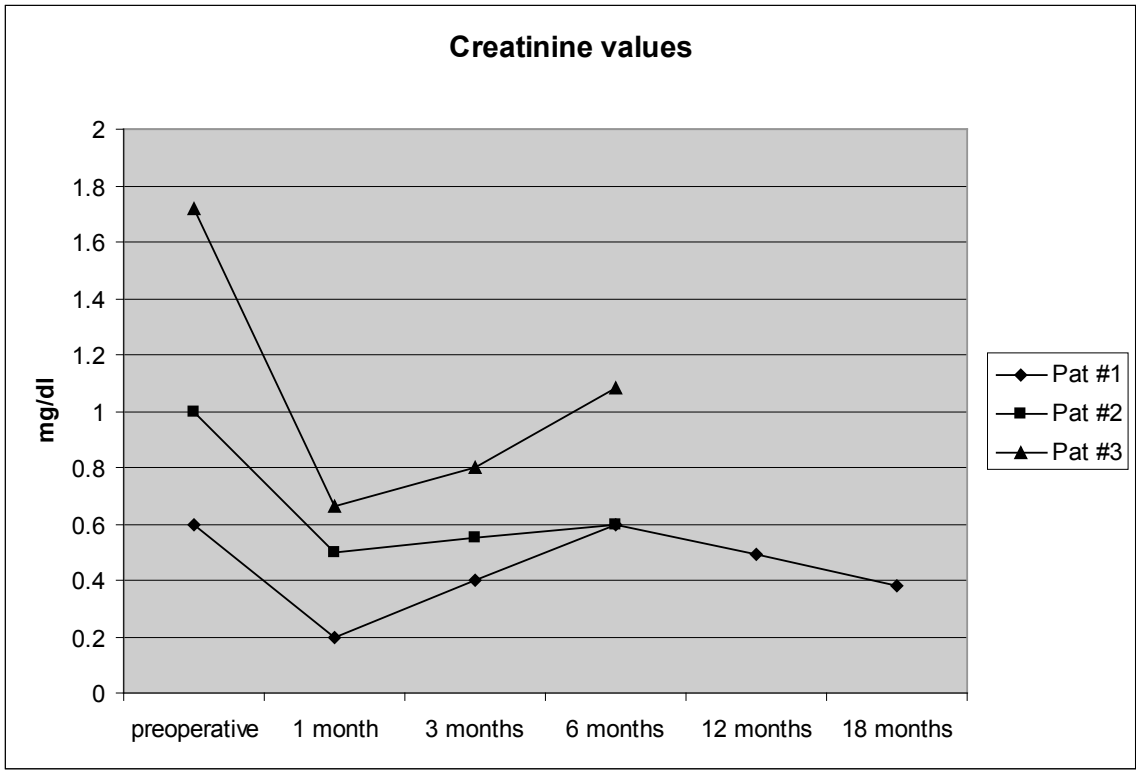

Figure 5 - Course of cratinine values in mg/dl for patient #1 to #3

Further complications were panic attacks (n:1, #1), psychic triggered vomiting (n:1, #2) and depression (n:1, #3). Recurring vomiting occurred in three patients (#1, #2, #3).

Patients	Pat#1	Pat#2	Pat#3	Pat#4
Neurological complications	No	No	Cerebral Hemorrhage after 84d on support	No
Bleeding complications needing blood transfusions	No	No	No	Yes
Epistaxis (treated conservatively)	2 episodes	2 episodes	4 episodes	No
Resternotomy	No	No	No	5 times in 4d
Secondary sternum closure	No	After 1d on support	No	No
Pump chamber exchange				
Due to thrombosis	LVAD after 109d on support	RVAD after 185d on support	No	No
Due to membrane rupture	RVAD after 298d on support	No	No	No
Infections				
Drive-line infections needing i.v. antibiotics	Recurring episodes with a support time over 6m	Recurring episodes with a support time over 6m	No	No
Other severe infections	No	No	2 episodes 1 leading to sepsis after 16d on support	No
Cause of death	No	No	Cerebral hemorrhage INR 2.8 PTT 72 sec. after 84d on support	Massive hemorrhage and multi-organ failure after 4d on support
HTx	After 545d on support	After 262d on support	No	No
Other complications	No	No	No	Post operative renal failure needing hemodialysis

Table 7 - Overview of complications during BVAD support

3.6 HU status, HTx and post HTx-course

Patient #1 was listed high urgent after 65 days on support and overall he was listed high urgent 480 days and three of four donor hearts were rejected. Patient #2 was listed high urgent after 242 days on BVAD support and transplanted 20 days later. Patient #3 was listed high urgent for a time of 95 days; from 10 days before BVAD implantation to death.
As you can see in the table above, two patients (#1, #2) were successfully transplanted after 545 and 262 days.
Complications in the post-transplantation course: reactivation of EBV (#1) and CMV (#2) infection responsive to antiviral treatment, thrombosis of the vena cava superior (3 weeks after HTx, #1), removed mechanically, rejection reaction grade II (26 days after HTx, #2) successfully treated and hemorrhagic colitis (one year after HTx, #2).

4 Discussion

This study reports on the experiences with the Berlin Heart Excor BVAD as BTT at the Medical University Graz, Division for Cardiac surgery. Contrary to children, in adults where MCS support has evolved drastically over the last decades with the introduction of intracorporal flow devices, experience with MCS in children is still limited due to several reasons. Most centres have experience with ECMO, as short-term support for postcardiotomy heart failure as BTR but its use is limited to a few days before serious complications like bleeding may occur. (40) In adults a large variety of adult sized VADs have been proven to be safe for long-term support (31) but there is only a small number of VADs, like the Berlin Heart Excor available for patients with a BSA less than 1.2 m^2 or body weight less then 20 kg (29). Also there is limited experience with pediatric long-term VADs most likely because terminal heart failure in children occurs rarely compared to adults.

Differences in the pathophysiology of heart failure in children (congenital heart defects, idiopathic cardiomyopathy) compared to adults (coronary heart disease) may lead to a less aggressive approach in many institutions when initiating MCS in children.

Overall outcome.

Whereas in adult patients numbers of BVAD implantation is declining (62,63), the incidence of biventricular heart failure in children remains high with 29% to 43% (29,40). This refers to the difference in pathophysiology of terminal heart failure in children, especially the high prevalence of right heart failure in children. Fan et al. found that children on biventricular support had significantly higher postoperative mortality than children on LVAD support. Preoperative milrinone should enhance right ventricular function and therefore reduce the need for BVAD support consequently leading to improved postimplantation survival. (64,65)

According to the published literature where BVAD support was found to be an independent risk factor for mortality (29), we found in our population a 25% 30 day mortality and 50% mortality before successful transplantation.

In children with cardiogenic shock ECMO remains as the first line MCS for bridge to either bridge, transplantation or recovery.

Imamura et al. examined outcomes in pediatric patients bridged to transplantation on ECMO versus Berlin Heart Excor support. Survival to transplant, recovery or continued support was 57% in ECMO and 86% in the Berlin Heart Excor group. Patients supported with the Berlin Heart Excor had a significantly better overall survival. (66)

Similar to Morales et al. we experienced a high percentage of patients supported with ECMO prior to VAD implantation (29) showing the severe illness of this patient collective. Fan et al. reported that congenital etiology, pre-operative norepinephrine requirement, high CRP level >6.3 mg/dl and central venous pressure >17 mmHg were associated with an increase in-hospital mortality in children with VAD support. Compared to our study with an overall survival of 50%, overall survival to transplantation or recovery was 63%, but in children, who were prior to VAD implantation supported with another MCS, overall survival was 47,1%. (67)

Even though VAD support is associated to a high complication rate, the post-transplantation outcome is as good as in children without cardiac support prior to HTx. (68,69) Referring to our study; the two patients who were successfully transplanted are currently at home and doing well.

Yu et al. found out that systemic inflammatory response (SIR) measured by CRP occurs in children prior to LVAD or BVAD Berlin Heart EXCOR implantation. All patients in that study, who were on BVAD support, had prior ECMO support. Further VAD implantation was related to significant increase in CRP and decrease in lymphocyte count referring to SIR and suppressed immune status (70), showing also the severe illness of this patient population.

Ayik et al. reported about children either supported with Berlin Heart Excor to HTx or immediate heart transplanted. Three out of 11 children were successfully bridged to transplantation with a LVAD Berlin Heart EXCOR, two children were still on support and six were primary heart transplanted. Similar to Gandhi severe complications on VAD support did not occur, mentioned complications were two episodes of minor drive-line infections. Overall pediatric transplantation mortality was 9.1% (1/11), one patient died three weeks after HTx due to biventricular and multi-organ failure. (71)

Another important point for the overall survival is the underlying cause of end-stage heart failure in children. Studies have shown that children with decompensated heart

insufficiency due to congenital heart defects have a lower post-implantation survival than those with no congential-etiology. (65,72,73)

Nevertheless the Berlin Heart EXCOR remains the only long-term live saving MCS in small children with biventricular failure. BVAD might not be only associated with a higher mortality but also with higher complication rate compared to LVAD support. (74)

Complications.

Complications occurring after months on BVAD will effect quality of life and outcome after HTx and are therefore of high interests for the children, parents and doctors. The initial North American multicenter study by Morales did not report adverse events such as stroke, thromboembolism, or infection, and device malfunctions. (29) In the US investigational device exemption trial, investigating the safety and efficacy of the Berlin Heart EXCOR pediatric VAD, adverse event rates have been mentioned but LVAD and BVAD were mixed together. (40) We wanted to focus solely on complications on BVAD. Stein et al. reported that children on VAD support who died before transplantation had significantly more adverse events per day on support than those, who were successfully transplanted, which is reflected by our study. (75)

Thrombembolic complications

Thrombembolic events and bleeding complications are the most frequent complications on long-term VAD, as described by different centers. (40,50,76) Therefore anticoagulation remains a matter of debate. In the initial North American experience no consistent anticoagulation protocol was mentioned. The US investigational device trial agreed to the Edmonton protocol, which proposes a 3-drug regimen involving aspirin, persantine and enoxaparin or oral anticoagulation similar to the anticoagulation protocol used at our center. (29) In our patient collective one patient died due to postoperative bleeding and one died due to cerebral hemorrhage; no other thrombembolic events related to BVAD were identified.

Malaisrie in the Initial Stanford Expirience reported frequent neurologic events, which occurred in five out of eight patients and were possibly caused by an anticoagulation regime different from the one used in Berlin.(22) At the same time Gandhi et al. had different results, eight out of nine patients were successfully bridged to HTx and complications like thromboembolic events, acute neurological complications, bleeding complications or detectable significant hemolysis did not arise. Drive-line infection in one

patient, pump chamber exchange in five patients and renal failure leading to death in one patient were the mentioned complications. (77) Brancaccio et al. reported 40% of neurologic events in their study similar to the Initial Stanford Expirience and death occurred in three out of four patients due to neurologic events and in one due to sepsis. Three out of ten patients were BVAD supported, all diagnosed with dilatative cardiomyopathy. In this BVAD supported group two patients died, one due to cerebral hemorrhage, one due to cerebral air embolism after pump chamber exchange and only one was successfully bridged to HTx. (78)

Recently Frazier et al. revealed 46 pump chamber exchanges in 48 patients identifying thrombus formation as most frequent cause. (40) Similar to Frasier, Gandhi reported about 12 total pump exchanges due to fibrin deposits or thrombus formation in five out of nine patients. (77) In our population we had to exchange pump chambers in two patients after 100 days or more on support due to thrombus formation. In patient #3 thrombus formations were detected on the right side pump chamber but not on the left. Increasing the anticoagulation sufficiently treated this thrombus formation; nevertheless we cannot completely exclude undetectable thrombus formation on the left pump chamber leading to silent cerebral infarction leading to subsequent cerebral hemorrhage.

Infection complications

Drive-line infections are still common; we noticed drive-line infections which had to be treated by intravenous antibiotics in both patients being on BVAD support for more than six months.

Attanaki et al. reported about a 35 years old male patient on Berlin Heart Excor biventricular support, who developed sepsis with splenic infarction after nine months on support due to septic embolization caused by a Staphylococcus aureus infection, therefore leading to urgent total spleenectomy and in the end successful treatment with heart transplantation in an emergency setting. (79) In our study two weeks after support one patient developed sepsis with septic thrombi in kidney, spleen and lungs, leading to re-intubation. Our patient recovered from this episode and was extubated two weeks later.

Holman et al. reported about infections on VAD support in adults and experienced that up to 25% of deaths in VAD supported patients are due to systemic sepsis. (80) Furthermore he reported that smaller implanted blood pumps have a lower risk for infection than larger implanted pumps. (81) It seems obvious that smaller contacting surfaces and fully implantable devices have a lower risk of infection. However the Berlin Heart Excor still

remains the only option for biventricular support in small children and therefore it is of definite interest to evolve small fully implantable devices adjustable to small patients.

Other complications

In our study three children suffered from mental stress during their time on BVAD support. Gilmore et al. interviewed children and their parents about their experiences on VAD support. Different experiences were described, from fear to trust toward the device. (82)

Similar experiences in occurrence and type of complications, as with our study, were reported from different centers. (65,83-86)

Future

The PediaFlow Pump is being developed, an implantable continuous flow pump the size of a double A battery. The impeller is elevated fully magnetically, therefore the impeller is the only blood-contacting surface and the attached power cord is the only skin penetrating part of this system. The PediaFlow Pump is conceived for chronic support, of up to six months, like the Berlin Heart, for patients from birth to two years of age (from 3 kg to 15 kg body weight). This system is still under development, but very promising for the future in pediatric long-term support. (87,88)

Conclusion. The EXCOR pediatric used as biventricular support is a life saving mechanical circulatory support system usable for mid to long term-support in children. It is still associated with a higher mortality compared to LVAD. Thromboembolic events, bleeding complications and drive line infection are still limiting factors. Further evolvement of implantable small devices for long-term support is of high interest; especially because of the potential good survival results in pediatric patients after HTx.

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Appendix 1 – Ethics committee vote

Ethikkommission

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VOTUM

gültig bis 20.04.2013

EK-Nummer:	24-322 ex 11/12
Studientitel:	Experience with Berlin Heart Excor Biventrivular support in children
Prüfer:	Prof.Dr. Karl-Heinz Tscheliessnigg Univ.Klinik für Chirurgie
Sponsor: *)	Med. Uni Graz
Ansprechpartner:	Julia Schrempf, ,
CRO:	-

*) Antragsteller

Die o.a. Studie wurde von der Ethikkommission erstmals im 'expedited Review' am 02.04.2012 behandelt. Die Ethikkommission ist zu folgendem Schluss gekommen:

Es besteht kein Einwand gegen die Durchführung der Studie in der vorliegenden Form.

Kommissionsmitglieder, die für diesen Tagesordnungspunkt als befangen anzusehen waren und daher gemäß Geschäftsordnung an der Entscheidungsfindung und Abstimmung nicht teilgenommen haben: keine

Zur Beurteilung vorliegende Dokumente:

Dokumente eingegangen am 28.03.2012, begutachtet im 'expedited Review' am 02.04.2012		
	Antragsformular	22.03.2012
	Originalprotokoll 1	18.03.2012
Dokumente eingegangen am 13.04.2012, begutachtet im 'expedited Review' am 20.04.2012		
✓	Antragsformular	
✓	Originalprotokoll 2	10.04.2012

Die Ethikkommission geht - rechtlich unverbindlich - davon aus, dass es sich um keine klinische Prüfung nach AMG bzw. MPG handelt.

Es handelt sich um eine Studie im Rahmen einer Diplomarbeit.

Das Votum der Ethikkommission berührt in keiner Weise die alleinige Verantwortung der Prüferin / des Prüfers / der Prüfer für die ordnungsgemäße Durchführung der Studie unter Einhaltung aller einschlägiger gesetzlicher Bestimmungen und Richtlinien.

Weiters machen wir darauf aufmerksam, dass der Kommission unverzüglich zu melden sind:

- Abweichungen vom Protokoll aus Sicherheitsgründen oder Protokolländerungen

- Änderungen, die das Risiko der Teilnehmer/-innen erhöhen oder die Durchführung der Studie wesentlich beeinflussen

- Mutmaßliche unerwartete schwerwiegende Nebenwirkungen - SUSARs (AMG-Studien ab 1.5.2004) oder schwerwiegende unerwünschte Ereignisse - SAEs (andere Studien)

- Jegliche Information über sonstige Umstände, die die Sicherheit der Teilnehmer/-innen oder die Durchführung der Studie beeinträchtigen können

Dieses Votum gilt für ein Jahr ab dem Datum der Ausstellung. Bei längerer Studiendauer ist rechtzeitig vor Ablauf der Gültigkeit des Votums ein Zwischenbericht vorzulegen (Berichtsformular), um eine etwaige Verlängerung zu erlangen.

Graz, 20. April 2012

Univ.Prof.DI Dr.Peter H. Rehak
Vorsitzender

Univ.Prof.DDr.Hans-Peter Kapfhammer
Stv. Vorsitzender

Achtung: Bitte bei allen das Projekt betreffende Schreiben oder telefonischen Anfragen die EK-Nummer angeben!

Medizinische Universität Graz, Auenbruggerplatz 2, A-8036 Graz. www.medunigraz.at

Appendix 2 – Poster presentation (Austrotransplant 2012)

Experiences with
Berlin Heart Excor Biventricular support in children

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Medical University of Graz

Background. The Berlin Heart Excor is a pneumatically driven VAD used as left, right or biventricular support. There are various pump volumes optimally designed for the needs of the patient from newborns to adolescents (ranging from 10 ml to 80 ml). We report our experiences with the Berlin Heart EXCOR System used as biventricuclar ventricular assist device (BVAD).

Methods. Between 2006 and 2012 four patients below 18 years of age (6ys, 14ys, 14ys,17ys) were treated with the BVAD Excor system. Implantation technique was: inflow cannula left was implanted at apex of the left ventricle and the outflow graft was anastomosed to the ascending aorta. On the right side inflow cannula was implanted in the right atrium, outflow cannula to the pulmonary trunk. Preoperative date may be seen in Table 1

Anticoagulation medication

-> Postoperatively i.v. heparin was started when no severe bleeding (target aPTT of 60 to 80 sec)
-> Acetylsalicylic acid (0,5mg/kg/day) as soon as all drains were removed (ARA < 30%)
-> Dipyridamol (3x75mg/day)
-> Coumadin on the normal ward (target INR 3.0 to 3.5)

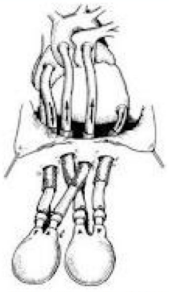

Figure 1. Berlin Heart Excor System (1)

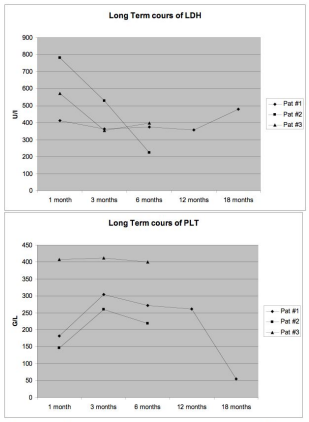

Figure 2. Course of hemolysis parameter (LDH, Platelets) for patient 1 to 3.

		Pat 1	Pat 2	Pat 3	Pat 4
Age	ys.	6.5	13.5	16.5	14
Gender	male/female	male	male	male	male
Diagnosis		DCMP	Postcardiotmy failuer	DCMP	Heart failure unknow
Year of Implant		2010	2009	2006	2012
BMI	kg/m²	12.4	19.5	20.3	15.6
Intermacs Level	(1-7)	1	1	2	2
mean BP	mmHG	60	55	80	60
Creatinine	mg/dl	0.6	1	1.7	0.72
Bilirubin	mg/dl	0.82	1.2	1.06	2.39
HB	g/dl	12.5	11.1	12.1	10.9
CVP	mmHg	9	16	20	15
LVEF	%	20	15	25	25
LVEDD	mm	44	55	73	41
TI	Grad	2	1	2	0
Inotropic support		Yes	Yes	Yes	Yes
ECMO support (days)			2		7

Table 1. Preoperative data of 4 patients undergoing EXCOR implantation.

Patients	Pat#1	Pat#2	Pat#3	Pat#4
Neurological complications	No	No	Cerebral Hemorrhage after 84d on support	No
Bleeding complications needing blood transfusions	No	No	No	Yes
Epistaxis (treated conservatively)	No	2 times	4 times	No
Resternotomy	No	No	No	5 times in 4d
Secondary sternum closure	No	After 1d on support	No	No
Pump chamber exchange				
Due to thrombosis	LVAD after 109d on support	RVAD after 185d on support	No	No
Due to membrane rupture	LVAD after 298d on support	No	No	No
Infections				
Drive-line infections needing i.v. antibiotics	Recurring episodes with a support time over 6m	Recurring episodes with a support time over 6m	No	No
Other severe infections	No	No	2 episodes 1 leading to sepsis after 16d on support	No
Cause of death	No	No	Cerebral hemorrhage INR 2.8 PTT 72 sec. after 84d on support	Massive hemorrhage and multi-organ failure after 4d on support
HTx	After 545d on support	After 262d on support	No	No
Other complications	No	No	No	Post operative renal failure needing hemolysis

Table 2. Outcome and complication profile during BVAD support

Discussion. Similar to Morales et al. we experienced a high percentage of patient supported with ECMO prior to VAD implantation (2) showing the severe illness of the patient collective.
The initial North American multicentre study by Morales did not report adverse events such as stroke, thromboembolism, or infection, and device malfunction. (2)
In the US investigational device exemption trial, investigating the safety and efficacy of the Berlin Heart EXCOR Pediatric VAD, adverse event rates have been mentioned but LVAD as well as BVAD were mixed together. (3)
Thromboembolic events and bleeding complications are the most frequent complications on long term VAD, followed by drive.line infections, similar to our patient collective and therefore a matter of debate.
Recently Fraser et al. revealed 46 pump changes in 48 patients identifying thrombus formation as the most frequent cause. (3). In our population we had to exchange pump chambers in two patients. In patient #3 thrombus formation were detected on the right-sided pump chamber but not on the left, treated with increased anticoagulation. We cannot completely exclude undetectable thrombus formation on the left pump chamber leading to silent cerebral infarction resulting in subsequent cerebral hemorrhage in patient #3.
The US investigational device trial agreed on the Edmonton protocol, which proposes a 3-drug regimen involving aspirin, persantine and enoxaparin or oral anticoagulation similar to the anticoagulation protocol use at our centre. (2)

Conclusion. The EXCOR is a live saving MCS system usable as paracoproral biventricular assist device for long term support. Thromboembolic events, bleeding complications and drive line infection are still limiting factors.

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