World Journal for Pediatric and Congenital Heart Surgery
2020, Vol. 11(3) 275-283

DOI: 10.1177/2150135120902114
journals.sagepub.com/home/pch


Pediatric Ventricular Assist Device Support in the Netherlands

Sofie Rohde, BSc[1], Christiaan F. J. Antonides, MD[1], Rahatullah Muslem, PhD[1], Pieter C. van de Woestijne, MD[1], Marijke H. van der Meulen, MD[2], Ulrike S. Kraemer, MD[2,3], Michiel Dalinghaus, MD, PhD[2], and Ad J. J. C. Bogers, MD, PhD[1]

Abstract

Background: This study aimed to evaluate the changes in heart transplantation (HTx) waiting list mortality following the introduction of the Berlin Heart EXCOR (BH EXCOR) in the Netherlands, as well as the occurrence of adverse events in these children. **Methods:** A retrospective, single-center study was conducted including all pediatric patients ($\leq$18 years) awaiting HTx. Patients were grouped in two eras based on availability of the BH EXCOR in our center, era I (1998-2006; not available) and era II (2007 to July 31, 2018; available). **Results:** In total, 87 patients were included, 15 in era I and 72 in era II. Extracorporeal membrane oxygenator support was required in 1 (7%) patient in era I and in 13 (18%) patients in era II. Overall mortality (7/15 in era I vs 16/72 in era II; 47% vs 22%, $P = .06$) and transplantation rates (8/15 in era I vs 47/72 in era II; 53% vs 65%, $P = .39$) did not differ significantly. Eleven (39%) patients of the pediatric ventricular assist device (VAD) population died, with the predominant cause being cerebrovascular accidents (CVAs) in eight (29%) patients. Furthermore, 14 (50%) of the pediatric VAD patients survived to transplantation. Adverse events most frequently occurring in VAD patients included CVA in 14 (50%), mostly (68%) within 30 days after VAD implantation, and bleeding requiring rethoracotomy in 14 (50%), all within 30 days after VAD implantation. **Conclusions:** The introduction of the BH EXCOR has positively impacted the survival of pediatric patients with end-stage heart failure in our center. The predominant cause of death changed from end-stage heart failure in era I to CVA in era II. We emphasize the need for large prospective registry–based studies.

Keywords

circulatory assist devices, pediatric, outcomes, heart transplantation

Submitted August 23, 2019; Accepted December 20, 2019.

Introduction

Ventricular assist devices (VADs) are an accepted therapy to bridge children with end-stage heart failure, predominantly caused by dilated cardiomyopathy (DCM), to heart transplantation (HTx) or recovery.[1] Over time, the use of VADs has increased to such an extent that, during the last decade, 25% of the pediatric HTx recipients received VAD support prior to HTx,[2] while this percentage is even higher (>50%) for pediatric patients with end-stage heart failure due to DCM.[3]

Ventricular assist device support has become a standard therapy in adult patients for end-stage heart failure, both as a bridge to transplantation or as a destination therapy, resulting in a significant reduction of the waiting list mortality.[4] Therefore, it is assumed that VAD support might offer an approach for the high waiting list mortality, 20% being reported in the United States and Europe, among pediatric patients.[5-7]

The Berlin Heart EXCOR Paediatric (Berlin Heart Gmbh, Berlin, Germany) is the most frequently used VAD in the pediatric population.[8] This is a paracorporeal, pneumatically driven VAD, specifically designed for children. Although this device has proven its merits, high rates of adverse events are reported. Specifically, thromboembolic events including ischemic cerebrovascular accidents (CVAs) and pump thrombosis resulting in device malfunction.[9-12]

[1] Cardiothoracic Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands
[2] Pediatric Cardiology, Erasmus University Medical Center, Rotterdam, the Netherlands
[3] Pediatric Intensive Care Unit, Erasmus University Medical Center, Rotterdam, the Netherlands

Corresponding Author:
Ad J. J. C. Bogers, Thoraxcenter, Room RG-619/625, Erasmus University Medical Center, Dr Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands.
Email: a.j.j.c.bogers@erasmusmc.nl

Abbreviations

BH EXCOR	Berlin Heart EXCOR
BiVAD	biventricular assist device
CHD	congenital heart disease
CVA	cerebrovascular accident
DCM	dilated cardiomyopathy
ECMO	extracorporeal membrane oxygenator
HTx	heart transplantation
ICU	intensive care unit
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IQR	interquartile range
LVAD	left ventricular assist device
Pedimacs	Pediatric Interagency Registry for mechanical Circulatory Support
RVAD	right ventricular assist device
VAD	ventricular assist device

In the Netherlands, the National Pediatric Heart Transplantation program is executed by the Erasmus University Medical Center, Rotterdam, where the Berlin Heart EXCOR (BH EXCOR) was introduced in 2006. Following the introduction, we previously published our experience with the BH EXCOR and reported rates of serious adverse events comparable to the literature.[13]

In this study, we evaluate our decade of experience with the BH EXCOR, through evaluation of the changes in waiting list mortality following its introduction in the Netherlands, as well as the occurrence of adverse events in the children supported by a VAD.

Patients and Methods

Study Cohort and Data Collection

This study was approved by the local medical ethical committee (MEC-2018-1483). For this study, the medical records of all the pediatric patients ($\leq$18 years) listed for HTx or supported by a VAD between 1998 and July 31, 2018, in the Netherlands, were retrospectively reviewed. Patients were divided into two eras: era I (1998-2006): prior to the introduction of a pediatric VAD in our center, and era II (2006-2018), after the introduction of a pediatric VAD. Data regarding age, sex, weight, etiology, number of previous cardiac surgeries, and laboratory values were obtained at the time of listing. N-terminal pro brain natriuretic peptide (NT-proBNP) could not be obtained from patients in era I (1998-2006) because this measurement was not yet widely applied at that time. In addition, data regarding days in the hospital, use of mechanical ventilation, extracorporeal membrane oxygenator (ECMO), inotropic support, and the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) classification during listing were extracted from medical records. Furthermore, for VAD patients, data regarding the type of device (left or biventricular assist device [LVAD/BiVAD]), intensive care unit (ICU) stay after VAD implantation, chest tube drainage, and use of blood products during VAD support were collected.

Outcomes

Primary outcomes are all-cause mortality, HTx, and weaning from VAD support due to cardiac recovery. Secondary outcomes were only studied in VAD patients and consist of CVAs, major bleeding or pericardial effusion requiring rethoracotomy, sepsis/infection, right heart failure, renal dysfunction, hepatic dysfunction, and device malfunction including confirmed pump thrombosis requiring replacement (definitions adapted from INTERMACS).

Berlin Heart and Anticoagulation

In all patients, a BH EXCOR Paediatric VAD (Berlin Heart Gmbh) was implanted. The BH EXCOR chamber is available in six different sizes (10, 15, 25, 30, 60, or 80 mL) and can provide univentricular left or right (LVAD/RVAD) and BiVAD support.

All children on VAD support received anticoagulation and antiplatelet therapy following the Edmonton protocol.[14] In brief, pediatric patients were treated with unfractionated heparin, low-molecular-weight heparin, or acenocoumarol, in combination with dipyridamole and/or aspirin.[15,16]

Criteria for VAD Implantation and Explantation

Criteria for VAD implantation were (1) eligibility for HTx, (2) deterioration of the circulation under increasing dosages of inotropes and/or development of metabolic acidosis, and (3) development of end-organ failure other than the heart.

Children were weaned from VAD support if myocardial function improved sufficiently as confirmed by laboratory parameters (decrease in NT-proBNP levels) and echocardiography (reverse remodeling, increased shortening fraction, the adequate opening of the aortic valve). Pump flow was first decreased to carefully evaluate left ventricular ejection fraction and opening of the aortic valve, before a temporary, exploratory pump stop. Surgical explantation was performed if the temporary pump stop was tolerated well.

Statistical Analyses

Nonparametric numerical data are presented as median (interquartile range [IQR]) and were analyzed with the Wilcoxon rank-sum test. Categorical data are presented as proportions and were analyzed with the χ^2 test or the Fisher exact test, where appropriate. A competing risk analysis was performed with R (R Core Team, 2017; R Foundation for Statistical Computing, Vienna, Austria) for HTx, recovery, death, or ongoing VAD support using the "cmprsk" package. Kaplan-Meier curves were used to evaluate survival and CVA-free survival in VAD patients. Patients were censored at the time of HTx or weaning from the device. A P value of less than .05 was considered statistically significant. Except from the competing risk analysis, all statistical analyses were performed with International Business Machines Corporation Statistical Package for the Social Sciences statistics version 24 (Armonk, New York).

Table 1. Baseline Characteristics: Era I Versus Era II and Non-VAD Patients Versus VAD Patients in Era II.[a]

Characteristic	Era I (n = 15)	Era II (n = 72)	*P*	Non-VAD (n = 44)	VAD (n = 28)	*P*
At listing						
Age, median (IQR), year	10.3 (2.6-13.1)	11.0 (3.3-14.3)	.60	11.2 (3.5-15.2)	10.7 (2.9-13.0)	.36
Female sex, n (%)	6 (40%)	39 (54%)	.40	23 (52%)	16 (57%)	.69
Weight, median (IQR), kg	21.9 (12.0-36.3)	30.5 (12.0-46.2)	.37	30.5 (12.0-47.8)	29.9 (11.8-44.5)	.56
Diagnosis			.80			.06
DCM	11 (73%)	46 (64%)		24 (55%)	22 (79%)	
Myocarditis	0	1 (1%)		0	1 (4%)	
CHD	1 (7%)	3 (4%)		3 (7%)	0	
Other	3 (20%)	22 (31%)		17 (39%)	5 (18%)	
Previous cardiac surgery			.50			.45
1	2 (13%)	4 (6%)		1 (2%)	3 (11%)	
2	0	6 (8%)		4 (9%)	2 (7%)	
3	1 (7%)	4 (6%)		3 (7%)	1 (4%)	
Serum creatinine, median (IQR), μmol/L	43 (29.0-52.0)	50.5 (33.3-63.8)	.33	50.5 (34.3-64.8)	51 (32.3-62.3)	.90
eGFR categories			.38			.66
<30% predicted	0	1 (1%)		1 (2%)	0	
30%-99% predicted	7 (47%)	46 (64%)		27 (61%)	19 (68%)	
>99% predicted	8 (53%)	25 (35%)		16 (36%)	9 (32%)	
Total bilirubin μmol/L			1.00			.36
<16 μmol/L	6 (40%)	37 (51%)		19 (43%)	18 (64%)	
>16 μmol/L	5 (33%)	27 (38%)		17 (39%)	10 (36%)	
NT-pro-BNP, median (IQR)	–	1016 (380.5-2071.5)		569 (269.5-1156.5)	1993 (1175.0-3916.0)	<.001
During listing						
Mechanical Ventilation	4 (27%)	13 (18%)	.48	8 (18%)	5 (18%)	1.00
ECMO only	1 (7%)	2 (3%)	.45	2 (5%)	–	<.001
ECMO prior to VAD support	–	11 (15%)		–	11 (39%)	
Inotropic support n (%)	12 (80%)	47 (65%)	.37	21 (48%)	26 (93%)	<.001
INTERMACS			.53			<.001
I	1 (7%)	2 (3%)		2 (5%)	0	
II	6 (40%)	36 (50%)		8 (18%)	28 (100.0%)	
III	4 (27%)	10 (14%)		10 (23%)	0	
IV	4 (27%)	24 (33%)		24 (55%)	0	
Days listed (IQR), days	53 (19.0-129.0)	56.5 (22.0-198.5)	.70	81 (23.0-292.5)	43 (21.3-123.3)	.12
% of hospital stay during listing (range), days	83.00% (0.0-100.0)	57.20% (0.0-100)	.50	4.60% (0.0-100.0)	100.00% (57.0-100.0)	<.001
0%-25%	4 (27%)	32 (44%)	.51	32 (73%)	0	<.001
26%-50%	0	2 (3%)		2 (5%)	0	
51%-75%	2 (13%)	6 (8%)		2 (5%)	4 (14%)	
76%-100%	9 (60%)	32 (44%)		8 (18%)	24 (86%)	

Abbreviations: CHD, congenital heart disease; CMP, cardiomyopathy; DCM, dilated cardiomyopathy; ECMO, extracorporeal membrane oxygenator; eGFR, estimated glomerular filtration rate; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IQR, interquartile range; NT-pro-BNP, N-terminal pro brain natriuretic peptide; VAD, ventricular assist device.

[a]Other CMP era I: restrictive cardiomyopathy 2, anthracycline induced 1. Other CMP non-VAD patients era II: restrictive cardiomyopathy 8, hypertrophic cardiomyopathy 3, noncompaction cardiomyopathy 2, right ventricle failure 2, arrhythmia 2. Other CMP VAD patients era II: restrictive cardiomyopathy 2, noncompaction cardiomyopathy 2, hypertrophic cardiomyopathy 1, myocarditis 1.

Results

Patient Characteristics: Era I Versus Era II

A total of 87 patients were included. In era I, before the introduction of the BH EXCOR in our center, 15 patients were listed with a median age of 10.3 years (IQR: 2.6-13.1).

In era II, between 2006 and July 2018, 72 patients were listed with a median age of 11.0 years (IQR: 3.3-14.3). There were no significant differences in baseline characteristics between patients in era I and era II (Table 1). Dilated cardiomyopathy was the most frequent etiology of heart failure both for patients in era I and for VAD patients in era II (Figure 1).

Primary Outcomes: Era I Versus Era II

Seven (47%) of 15 patients died in era I and 16 (22%) of 72 in era II ($P = .06$); furthermore, HTx was realized in 8 (53%) of 15 patients in era I and 47 (65%) of 72 patients in era II ($P = .39$). At the end of the study period, 7/72 (10%) patients

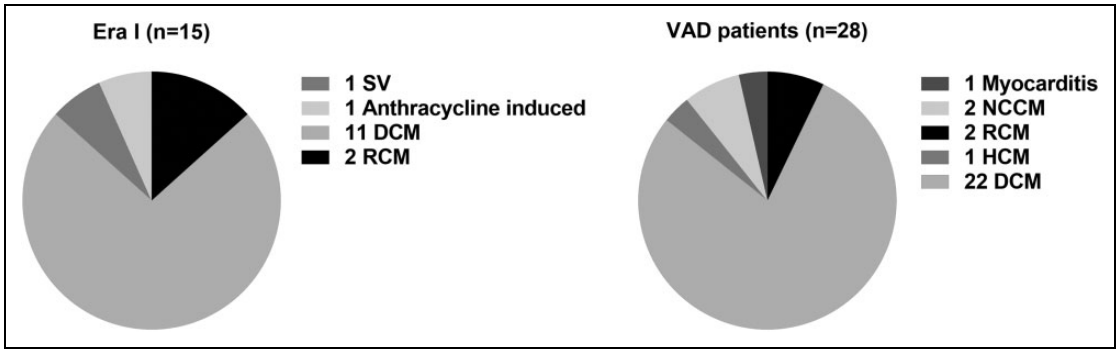

Figure 1. Etiology distribution per subgroup. DCM indicates dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; NCCM, cardiomyopathy; RCM, restrictive cardiomyopathy; RV, right ventricle; SV, single ventricle; VAD, ventricular assist device.

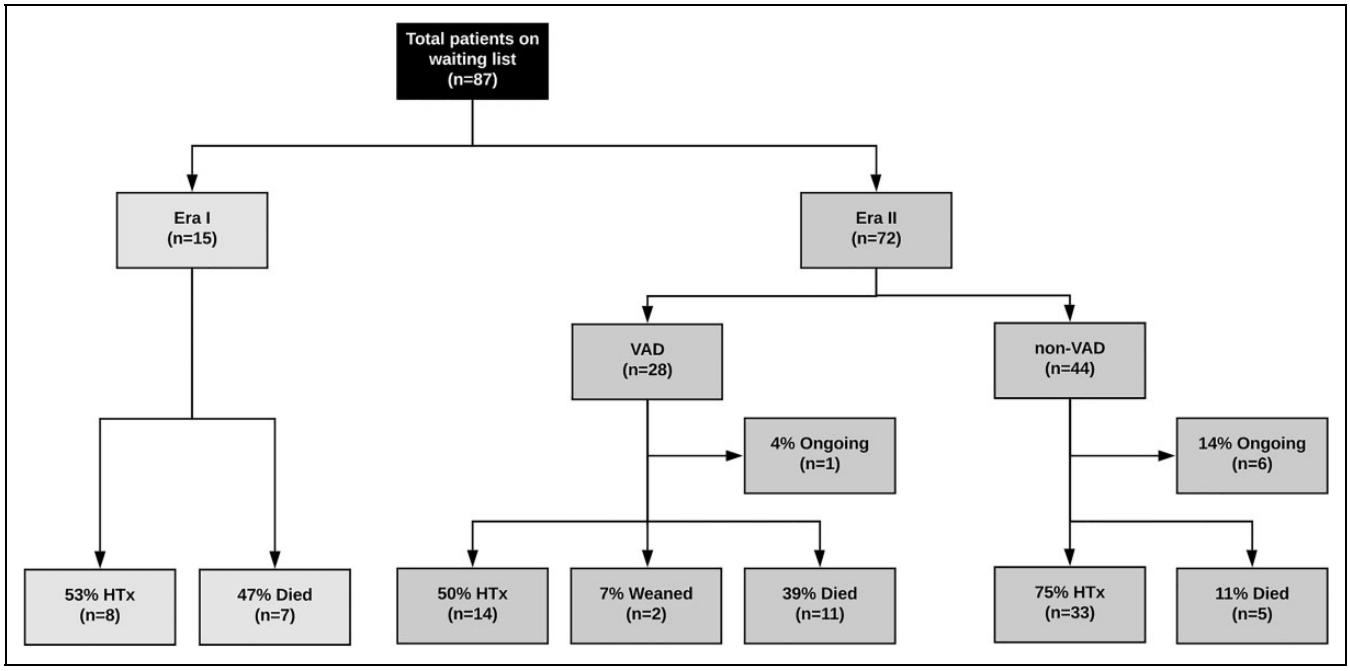

Figure 2. Primary outcomes of all patients listed. HTx indicates heart transplantation; VAD, ventricular assist device.

in Era II were still on the waiting list, 6 (8%) non-VAD patients and 1 (1%) VAD patient requiring ongoing VAD support. Finally, 2 (7%) of 28 patients were weaned of VAD support due to myocardial recovery during the study period (Figure 2).

Causes of death differed in era I from era II, with end-stage heart failure being the predominant cause of death in era I and CVA in era II (Table 2).

Ventricular Assist Device Versus Non-VAD Patients in Era II

In era II, 28 (39%) of the 72 patients were supported by a VAD. All patients were cannulated apically, except one. In this patient, the left atrium was cannulated because of the anticipated vulnerability of the left ventricular apex due to the presence of myocarditis and pericarditis. Ventricular assist device implantation was often preceded by ECMO support (n = 11, 39%).

Furthermore, VAD patients required inotropic support more frequently (93% vs 48%, $P < .001$) and had a worse INTERMACS classification ($P < .001$) compared to non-VAD patients. Of the VAD patients, 24 (86%) were hospitalized for a period of 76% to 100% (median: 33 days, IQR: 21-68) during listing; of these patients, 23 were hospitalized for the complete duration of the listing period. A significant part of those patients had to be hospitalized because a mobile driver was not available. In the non-VAD patients, eight (18%) were hospitalized for the complete duration of the listing period (Table 1). In contrast, of the non-VAD patients, 22 (50%) remained at home during the whole listing period.

The majority of VAD patients were supported by a LVAD (89%) and three (11%) patients were supported by a BiVAD. The median duration of VAD support was 37.0 days (IQR:

Table 2. Specific Cause of Death.

Causes of death	Era I (n = 15)	Era II (n = 72)	Non-VAD (n = 44)	VAD Patients (n = 28)
CVA	0	9 (13%)	1 (2%)	8 (29%)
Hemorrhagic		2	0	2
Pulmonary hemorrhage	0	1 (1%)	0	1 (4%)
Aortic bleeding	0	1 (1%)	0	1 (4%)
Recurrent thrombosis heart and pump	0	1 (1%)	0	1 (4%)
Pneumonia	2 (13%)	0	0	0
End-stage heart failure	5 (33%)	4 (6%)	4 (9%)	0

Abbreviations: CVA, cerebrovascular accident; VAD, ventricular assist device.

Table 3. VAD Patients.

Days on VAD, median (IQR), days	37.0 (12.3-123.0)
LVAD, n (%)	25 (89%)
BiVAD, n (%)	3 (11%)
ICU stay, median (IQR), days	35.0 (12.3-114.3)
Chest tube drainage, median (IQR), mL	1482.5 (286.3-3960.0)
Erythrocyte transfusions, median (IQR), mL	395.0 (0.0-915.0)
Thrombocytes transfusion, median (IQR), mL	0.0 (0.0-412.5)
Plasma transfusion, median (IQR), mL	225.0 (0.0-671.3)

Abbreviations: BiVAD, biventricular assist device; ICU, intensive care unit; IQR, interquartile range; LVAD, left ventricular assist device; VAD, ventricular assist device.

12.3-123.0). The median ICU stay after VAD implantation was 35.0 days (IQR: 12.3-114.3). Blood product utilization is reported in Table 3.

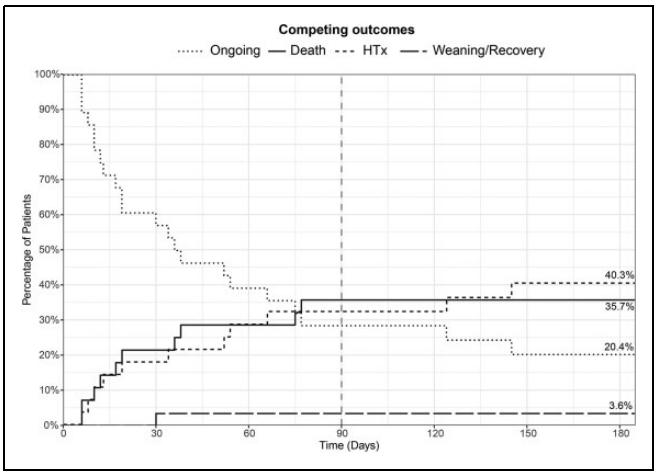

Figure 3. Competing outcomes analysis in VAD patients. VAD indicates ventricular assist device.

Primary Outcomes: VAD Patients Versus Non-VAD Patients in Era II

The all-cause mortality in VAD patients was 39% and 11% in non-VAD patients ($P = .01$) during a median time of listing of 56.5 days (IQR: 22.0-198.5). Furthermore, 14 (50%) of the VAD patients and 33 (75%) of the non-VAD patients underwent HTx ($P = .03$). Two (7%) patients were weaned from VAD support due to myocardial recovery (Figure 2). Both children were younger than one year and weighed less than 10 kg. At the end of the study period, seven (10%) patients in era II were still on the waiting list, six (8%) of them were non-VAD patients and one (1%) was still ongoing on VAD support.

Cerebrovascular accident was the predominant cause of death in VAD patients (8/11 patients; 73%). This is in contrast to non-VAD patients, in whom four (80%) of five died due to end-stage heart failure (Table 2). The parents of three deceased non-VAD patients declined VAD support. The fourth patient was considered unsuited due to the small size of the patient in combination with the complexity of the heart disease.

Outcomes in VAD Patients Only

Figure 3 depicts a competing outcomes analysis of the primary outcomes in all VAD patients (n = 28). The transplantation rate after 180 days was 40.3% and the mortality rate 35.7%. Two ventricular assist device patients (3.6%) were weaned off device and 20.4% were still ongoing.

During the study period, 19 CVAs occurred in 14 patients, 15 of them being ischemic CVAs. Most CVAs (68%) occurred within 30 days after VAD implantation. Extracorporeal membrane oxygenator support before VAD support did not increase the risk of CVAs ($P = 1.00$).

Fourteen patients required a rethoracotomy due to bleeding, and six of these patients required a second rethoracotomy. All bleedings requiring rethoracotomy occurred within 30 days after VAD implantation. Pump exchange was necessary 26 times in 15 patients, due to pump thrombosis in 22 (85%) cases, mechanical problems in 1 (4%) case, due to a tear in one of the cannulas in 1 (4%) patient, due to reaching the 800th cycles (4%), and after an ischemic CVA (4%). Of all, 62% of the exchanges took place >30 days of VAD implantation. Other adverse events included renal dysfunction in three (11%) patients, right heart failure in two (7%) patients (one requiring secondary RVAD support; Table 4). The complete list of adverse events per patient is listed in Supplemental Material 1.

Figure 4 depicts overall survival and CVA-free survival in VAD patients. The overall three-month survival was 54%, and the CVA-free survival at three months was 33%. Twelve of

Table 4. Adverse Events During VAD Support.

Adverse Event	Number of Events	Number of Patients Affected	<30 Days	>30 Days
CVA	19	14 (50%)	13 (68%)	6 (32%)
Ischemic	15			
Hemorrhagic	4			
Bleeding requiring rethoracotomy	20	14 (50%)	20 (100%)	0
Tamponade	8			
Pump exchange	26	15 (54%)	10 (38%)	16 (62%)
Due to thrombosis	22			
Due to mechanical problems	1			
Due to tear in the cannula	1			
Due to reaching the 800th cyclus	1			
After iCVA	1			
Renal dysfunction	3	3 (11%)	3 (100%)	0
Requiring dialysis	1			
Right heart failure	2	2 (7%)	2 (100%)	0
Requiring RVAD	1			
Sepsis	1	1 (4%)		

Abbreviations: CVA, cerebrovascular accident; iCVA, ischemic cerebrovascular accident; RVAD, right ventricular assist device; VAD, ventricular assist device.

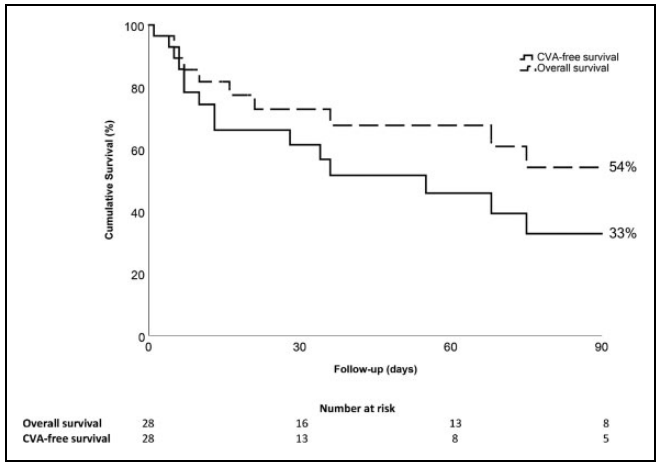

Figure 4. Kaplan-Meier function of the overall and CVA-free survival in VAD patient. CVA indicates cerebrovascular accident; VAD, ventricular assist device.

28 (43%) patients supported with a VAD survived to HTx or weaning without suffering a CVA.

Of the 14 patients who suffered a CVA, 8 (57%) died due to the CVA, 1 (7%) died due to an aortic bleeding, 3 (21%) were transplanted, and 2 (14%) were weaned off VAD support after myocardial recovery.

Comment

Since the introduction of the BH EXCOR in our center, we experience a trend toward lower mortality rates in pediatric patients awaiting HTx. However, adverse event rates continue to be high. Especially, thromboembolic complications and its consequences remain a significant concern.

The United Network of Organ Sharing database showed that since VAD therapy became more widely available, pediatric HTx waiting list mortality declined from 16% in 1999 to 2004 to 8% in 2005 to 2014.[17] For pediatric patients supported by a VAD, the Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) reported a VAD mortality of 19% at six months.[18] Similarly, the Paediatric European Registry for Patient with Mechanical Circulatory Support reports a mortality of 17% within two years of follow-up for pediatric VAD patients.[19] In comparison, in the adult population, INTERMACS reported a mortality of 13% at one year in patients who were implanted as a bridge to therapy strategy, while the EUROMACS registry reported a mortality of 27.9% at six months.[20,21]

Despite the promising trend toward a decrease in mortality on the pediatric HTx waiting list, the use of pediatric VADs is accompanied by a high rate of adverse events. Including pump exchanges due to pump thrombosis, CVA, and bleeding requires rethoracotomy.

The transparency of the pump chambers allows for thrombi to be detected directly, and if necessary, replacement is relatively easy since the pump is paracorporeal. The occurrence of CVA, on the contrary, is of major importance due to the devastating consequences in most cases. Incidence rates of 17% and 22% have been reported previously in larger cohorts.[10,22] One study[9] reported an incidence of ischemic CVA in 22% and cerebral hemorrhage in 47%. This study, however, included the earliest experience of VAD implantation between 1990 and 2000. Several changes in pump design took place in the last 30 years. Different stroke volume chambers were introduced and apical cannulation is now preferred over atrial cannulation, which improves left ventricle unloading,[23] which might partially explain the higher incidence of CVA. Our study reported a relatively high incidence of CVA (50%); however, our program only started in 2006. The high CVA rate might be explained by the relatively limited experience in our center.

Cerebrovascular accident rates reported in adult VAD patients are lower compared to the pediatric patients.[21] The

difference in CVA rates between an adult and pediatric VAD supported patient may be due to a variety of factors. Adults are mostly implanted with continuous-flow second- or third-generation pumps, in contrast to children, who are generally supported by the paracorporeal BH EXCOR. Furthermore, randomized control trials and anticoagulation studies have been performed primarily in the adult population due to the strict ethical restrictions to research in children and the small population of pediatric VAD patients per medical center.

The difference in thromboembolic event rate between adults and children might be explained by the differences in the hematological status. The administered anticoagulant drugs to prevent thrombus formation do not completely inhibit thrombin generation, leading to the consumption of several coagulation factors. This is one of the reasons why controlling coagulation in adult patients as well as in pediatric patients supported with a VAD is difficult.[24,25] In children, the issue is complicated by the fact that the coagulation system is still evolving and ever-changing. Quantitative as well as qualitative differences in coagulation factors compared to the adult population are present, and as a result, the interaction between anticoagulation drugs and coagulation factors between adults and children differs.[24] The magnitude of these differences is not yet fully understood, making it even harder to gain grip on the coagulation system of children supported with a VAD. Especially in children with congenital heart disease (CHD) supported by a VAD, this may be relevant because CHD is known to influence certain coagulation factors, creating an additional risk factor for an unbalanced coagulation system.[24,25]

In our center, pediatric VAD patients are anticoagulated following the Edmonton protocol, which is the best studied anticoagulation protocol used in pediatric VAD patients. However, a recent study reported great variation in adherence to the Edmonton Protocol.[26] Therefore, more research on anticoagulation in children supported with a VAD is warranted. Unfortunately, randomized control trials comparing different anticoagulation protocols in this pediatric population will probably be unrealistic due to ethical concerns and small patient numbers per medical center. Prospective registry-based studies comparing the different anticoagulation protocols, already being used in hospitals over the world, are required to provide sufficient evidence, which can be used as evidence to guide new protocols.

Several laboratory coagulation parameters, measured preoperatively and multiple times postoperatively, should be included in this database. Given that the results of conventional tests such as international normalized ratio, activated partial thromboplastin time, and platelet count can turn out normal during the occurrence of thromboembolic complications, thromboelastography and aggregometry should therefore be added to this routine laboratory testing.[27]

An example initiative is ACTION (Advanced Cardiac Therapies Improving Outcomes Network), which has been set up to help physicians find out what the best anticoagulation strategy is.[28]

Finally, the higher incidence of thromboembolic events in children might also be due to the relatively late implantation in pediatric patients compared to a less conservative approach in adults. In children, 87% is classified as INTERMACS I or II,[18] and in our study, all children were classified as INTERMACS I or II. In contrast, in adults, just over 50% is classified as INTERMACS patient profile I or II.[29] During this critical clinical condition, multiple mechanisms of the immune system, several unknown or not fully understood, are activated causing changes in the activation of factors and thrombus formation, similarly as infections are known to influence coagulation.[30,31] This theory is supported by the difference in timing of adverse event rates according to the Pedimacs registry. The early adverse event rate (<90 days postimplant) was significantly higher than the late adverse event rate (>90 days postimplant; 109 vs 34.4 events per 100 patient-months, $P < .0001$).[32] Similarly, in our study, all of the bleedings require rethoracotomy and most of the CVAs (68%) occurred within the first 30 days after VAD implantation.

Optimal timing of VAD implantation, however, remains subject of debate. The range of time between implanting VADs too early, preventing irreversible end-organ damage, and implanting VADs too late, preventing a certain percentage of children to be implanted unnecessarily, is small and undefined.

Finally, another important issue of VAD therapy is a significant appeal to resources. The financial burden of VAD therapy, not only caused by the device (and possible exchanges) but also by the ICU stay after VAD placement, the total hospital stay during listing, the use of blood products, and the possible increased absenteeism of the parents at work, is huge. Moreover, the social impact on the child as on the family should not be underestimated.

Limitations

This observational study, although reporting on a national program, is limited by its single-center retrospective design and lack of randomization. Furthermore, the small study size, especially in era I, and the heterogeneous group of patients supported with the BH EXCOR warrant a cautious approach to interpretation of our observations. More research on specific age and etiology groups is warranted, especially in the smallest children requiring VAD support. Strengths of this study include the long follow-up period, the extensive description of the population admissible for VAD therapy, in addition to the comprehensive assessment of the adverse events and outcomes.

Conclusion

The introduction of the BH EXCOR has positively impacted the survival of pediatric patients with end-stage heart failure in our center. However, further improvement in pediatric VAD design is warranted. Finally, we emphasize the need for large prospective registry-based studies since the experience with and evidence of VAD support in children are expanding but remain limited.

Authors' Note

S.R. and C.F.J.A. contributed equally.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Supplemental Material

Supplemental material for this article is available online.

References

1. Morales DLS, Rossano JW, VanderPluym C, et al. Third Annual Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) report: preimplant characteristics and outcomes. *Ann Thorac Surg*. 2019;107(4): 993-1004.
2. Lund LH, Khush KK, Cherikh WS, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-Fourth Adult Heart Transplantation Report-2017; focus theme: allograft ischemic time. *J Heart Lung Transplant*. 2017; 36(10): 1037-1046.
3. Rossano JW, Cherikh WS, Chambers DC, et al. The Registry of the International Society for Heart and Lung Transplantation: Twentieth Pediatric Heart Transplantation Report-2017; focus theme: allograft ischemic time. *J Heart Lung Transplant*. 2017; 36(10): 1060-1069.
4. McIlvennan CK, Magid KH, Ambardekar AV, Thompson JS, Matlock DD, Allen LA. Clinical outcomes after continuous-flow left ventricular assist device: a systematic review. *Circ Heart Fail*. 2014;7(6): 1003-1013.
5. Almond CSD, Thiagarajan RR, Piercey GE, et al. Waiting list mortality among children listed for heart transplantation in the United States. *Circulation*. 2009;119(5): 717-727.
6. Mah D, Singh TP, Thiagarajan RR, et al. Incidence and risk factors for mortality in infants awaiting heart transplantation in the USA. *J Heart Lung Transplant*. 2009;28(12): 1292-1298.
7. Smits JM, Thul J, De Pauw M, et al. Pediatric heart allocation and transplantation in Eurotransplant. *Transpl Int*. 2014;27(9): 917-925.
8. Adachi I, Burki S, Zafar F, Morales DL. Pediatric ventricular assist devices. *J Thorac Dis*. 2015;7(12): 2194-2202.
9. Hetzer R, Kaufmann F, Delmo Walter EM. Paediatric mechanical circulatory support with Berlin Heart EXCOR: development and outcome of a 23-year experience. *Eur J Cardiothorac Surg*. 2016; 50(2): 203-210.
10. Cassidy J, Dominguez T, Haynes S, et al. A longer waiting game: bridging children to heart transplant with the Berlin Heart EXCOR device—the United Kingdom experience. *J Heart Lung Transplant*. 2013;32(11): 1101-1106.
11. Blume ED, Naftel DC, Bastardi HJ, Duncan BW, Kirklin JK, Webber SA. Outcomes of children bridged to heart transplantation with ventricular assist devices: a multi-institutional study. *Circulation*. 2006;113(19): 2313-2319.
12. Fan Y, Weng Y-G, Huebler M, et al. Predictors of in-hospital mortality in children after long-term ventricular assist device insertion. *J Am Coll Cardiol*. 2011;58(11): 1183-1190.
13. van der Meulen MH, Dalinghaus M, Maat AP, et al. Mechanical circulatory support in the Dutch National Paediatric Heart Transplantation programme. *Eur J Cardiothorac Surg*. 2015;48(6): 910-916; discussion 916.
14. Singh TP. Prospective trial of a pediatric ventricular assist device. *N Engl J Med*. 2012;367(22): 2159; author reply 2160-2151.
15. Rutledge JM, Chakravarti S, Massicotte MP, Buchholz H, Ross DB, Joashi U. Antithrombotic strategies in children receiving long-term berlin heart EXCOR ventricular assist device therapy. *J Heart Lung Transplant*. 2013;32(5): 569-573.
16. Almond CS, Buchholz H, Massicotte P, et al. Berlin heart EXCOR Pediatric ventricular assist device investigational device exemption study: study design and rationale. *Am Heart J*. 2011; 162(3): 425-435. e426.
17. Zafar F, Castleberry C, Khan MS, et al. Pediatric heart transplant waiting list mortality in the era of ventricular assist devices. *J Heart Lung Transplant*. 2015;34(1): 82-88.
18. Blume ED, VanderPluym C, Lorts A, et al. Second annual pediatric interagency registry for mechanical circulatory support (Pedimacs) report: pre-implant characteristics and outcomes. *J Heart Lung Transplant*. 2018;37(1): 38-45.
19. De By T, Schweiger M, Waheed H, et al. The European Registry for Patients with Mechanical Circulatory Support (EUROMACS): first EUROMACS Paediatric (Paedi-EUROMACS) report. *Eur J Cardiothorac Surg*. 2018;54(5): 800-808.
20. De By T, Mohacsi P, Gahl B, et al. The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) of the European Association for Cardio-Thoracic Surgery (EACTS): second report. *Eur J Cardiothorac Surg*. 2018;53(2): 309-316.
21. Kirklin JK, Naftel DC, Pagani FD, et al. Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant*. 2015;34(12): 1495-1504.
22. Weinstein S, Bello R, Pizarro C, et al. The use of the berlin heart EXCOR in patients with functional single ventricle. *J Thorac Cardiovasc Surg*. 2014;147(2): 697-704; discussion 704-695.
23. Hetzer R, Alexi-Meskishvili V, Weng Y, et al. Mechanical cardiac support in the young with the berlin heart EXCOR pulsatile ventricular assist device: 15 years' experience. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2006:99-108.
24. Ignjatovic V, Mertyn E, Monagle P. The coagulation system in children: developmental and pathophysiological considerations. *Semin Thromb Hemost*. 2011;37(7): 723-729.
25. Eaton MP, Iannoli EM. Coagulation considerations for infants and children undergoing cardiopulmonary bypass. *Paediatr Anaesth*. 2011;21(1): 31-42.
26. May LJ, Lorts A, VanderPluym C, et al. Marked practice variation in antithrombotic care with the berlin heart EXCOR pediatric ventricular assist device. *ASAIO J*. 2019;65(7): 731-737.
27. Gorlinger K, Bergmann L, Dirkmann D. Coagulation management in patients undergoing mechanical circulatory support. *Best Pract Res Clin Anaesthesiol*. 2012;26(2): 179-198.
28. Peng DM, Rosenthal DN, Zafar F, Smyth L, VanderPluym CJ, Lorts A. Collaboration and new data in ACTION: a learning

health care system to improve pediatric heart failure and ventricular assist device outcomes. *Transl Pediatrics*. 2019;8(4): 349-355.

29. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. *J Heart Lung Transplant*. 2017;36(10): 1080-1086.
30. Levi M, Keller TT, Van Gorp E, Ten Cate H. Infection and inflammation and the coagulation system. *Cardiovasc Res*. 2003;60(1): 26-39.
31. Hampton CR, Verrier ED. Systemic consequences of ventricular assist devices: alterations of coagulation, immune function, inflammation, and the neuroendocrine system. *Artif Organs*. 2002;26(11): 902-908.
32. Rosenthal DN, Almond CS, Jaquiss RD, et al. Adverse events in children implanted with ventricular assist devices in the United States: data from the Pediatric Interagency Registry for Mechanical Circulatory Support (PEDIMACS). *J Heart Lung Transplant*. 2016;35(5): 569-577.