Pediatric Mechanical Circulatory Support: Introduction and Schneider's Experience

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ABSTRACT **Background:** Ventricular assist devices (VADs) play a critical and increasing role in treating end-stage heart failure in pediatric patients. A growing number of patients are supported by VADs as a bridge to heart transplantation. Experience with VADs in the pediatric population is limited, and experience in Israel has not been published.

Objectives: To describe this life-saving technology and our experience with VAD implantation in children with heart failure, including characteristics and outcomes.

Methods: We conducted a retrospective chart review of all patients who underwent VAD implantation at Schneider Children's Medical Center from 2018 to 2023.

Results: We analyzed results of 15 children who underwent VAD implantation. The youngest was 2.5 years old and weighed 11 kg at implantation. In eight patients, HeartMate 3, a continuous-flow device, was implanted. Seven patients received Berlin Heart, a pulsatile-flow device. Three children required biventricular support; 11 underwent heart transplants after a median duration of 169 days. Two patients died due to complications while awaiting a transplant; two were still on VAD support at the time of submission of this article. Successful VAD support was achieved in 86.6% of patients. In the last 5 years, 79% of our heart transplant patients received VAD support prior to transplant.

Conclusions: Circulatory assist devices are an excellent bridge to transplantation for pediatric patients reaching end-stage heart failure. VADs should be carefully selected, and implantation techniques tailored to patient's weight and diagnosis at a centralized pediatric cardiac transplantation center. Israeli healthcare providers should be cognizant of this therapeutic alternative.

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KEY WORDS: end-stage heart failure, heart transplantation, mechanical circulatory support, pediatric, ventricular assist device

The treatment of pediatric patients with end-stage heart failure who need a heart transplant is constrained due to limited donor heart availability, long waiting lists, and high mortality while on the waiting list. The implantation of ventricular assist devices (VADs) as a bridge to heart transplantation in pediatric patients has increased significantly over the past two decades, reducing waitlist mortality by 50%. Current data suggest that approximately one-third of pediatric heart transplant patients were supported by VADs before transplant [1-5].

VADs are used in children as a bridge to transplantation, a bridge to recovery, a bridge to further decision and, in highly selected patients, as the destination therapy [6,7]. Implantation of VADs in the pediatric population presents many surgical and medical challenges. Low case volume, heterogeneous cardiac anatomy, and diverse patient age and size impact medical decisions and choice of device. The main diagnoses leading to heart failure and the possible need for VAD implantation are congenital cardiomyopathy, myocarditis leading to cardiomyopathy, and congenital heart defects [1,3].

The implantation of a VAD holds substantial risk for complications, although outcomes, including mortality rates, continue to improve. Reported adverse events include bleeding, infections, device malfunction, and neurological injury such as ischemic and hemorrhagic strokes [3,4,8,9]. Mechanical circulatory support (MCS) alters hemostatic balance. Blood exposure to non-endothelialized biomaterials induces consumption of anticoagulation factors and the production of procoagulants. Physical pump injury to red blood cells and shear stress forces cause hemolysis, which contributes to the clotting system activation. Pediatric patients supported by MCS are characterized by higher incidence of thrombotic and

hemorrhagic events compared to adult patients. This situation has prompted the development of several anticoagulation strategies to lower the risks [10].

Several MCS devices are available worldwide, with various properties distinguishing them [Table 1]. Devices differ by the flow they generate (pulsatile or continuous) and support configuration as some devices offer only left ventricular support, while others enable left, right, and biventricular support. Implantation sites include intracorporeal devices (the pump is implanted inside the patient's body), extracorporeal or paracorporeal devices (the pump is placed outside the body), and percutaneous devices (the device is implanted via a vascular approach). The anticipated duration of support also guides device selection, as some devices only provide temporary support, while others may provide support for a prolonged duration, even up to several years. Device selection must be tailored to the patient's size, cardiac anatomy, and the required support. Options for smaller children are limited due to their small thoracic space and cardiac ventricular cavity [4,6,11,12]. While the utilization of VADs in the pediatric population has increased considerably in the last two decades, this treatment option has only become available for children in Israel in recent years.

In this report we present our experience with VADs in a pediatric tertiary center in Israel. We aim to raise awareness of this emerging technology among Israeli caregivers and to offer more children suitable treatment at the appropriate time.

PATIENTS AND METHODS

STUDY POPULATION AND DATA COLLECTION

We conducted a retrospective analysis of all pediatric patients implanted with VAD at Schneider Children's Medical Center of Israel. Data were retrieved from electronic medical records of pediatric patients aged 0 to 18 years who underwent VAD implantation between October 2018 and May 2023. Patients supported by a temporary device were excluded from the analysis. The institutional review board approved the study and waved the need for informed consent. The data collected included demographics, preoperative diagnoses and characteristics, device type, perioperative characteristics, and postoperative course and outcome. Patient characteristics and clinical course were evaluated using descriptive statistics.

PRACTICE OF VAD IMPLANTATION AND PATIENT MANAGEMENT

Since the establishment of our VAD program, we have implanted two types of VADs: the Berlin Heart EXCOR® (Berlin Heart GmbH, Berlin, Germany) and the

Table 1. Commonly used pediatric mechanical circulatory support devices

	Flow type	Implantation site	Comments
Temporary mechanical circulatory support devices			
Rotaflow	Continuous flow	Paracorporeal	Usually part of the ECMO circuit
PediMag	Continuous flow	Paracorporeal	Approved for up to 6-hour use
CentriMag	Continuous flow	Paracorporeal	Approved for up to 30-day use
Durable mechanical circulatory support devices			
HeartMate 3	Continuous flow	Intracorporeal	The smallest patient implanted – 19 kg
HeartWare	Continuous flow	Intracorporeal	Manufacturing and distribution discontinued on June 21, 2021[12]
Berlin Heart EXCOR / Active	Pulsatile flow	Paracorporeal	Approved for patients weighing > 3 kg
SynCardia TAH	Pulsatile flow	Paracorporeal	Approved for patients with BSA > 1.2 m^2

Other VADs are still under clinical testing [11]
BSA = body surface area, ECMO = extracorporeal membrane oxygenation, TAH = total artificial heart

HeartMate 3™ (Abbott, Chicago, IL, USA). The Berlin Heart EXCOR is a CE and FDA-approved, pneumatically driven, pulsatile flow, paracorporeal VAD that can provide single or biventricular support. Its use is suitable even in small infants and newborns (over 3 kg). The Berlin Heart device has been implanted mainly in smaller children (< 20 kg) and in those who need biventricular support. Since January 2022 we have used the new Berlin Heart Active console, which received the CE mark in 2019 and which has major advantages over the older version [Figure 1].

The HeartMate 3, which received a CE mark in 2015 and FDA approval in 2017, is an intracorporeal continuous flow device that enables patient discharge and demonstrated fewer events of stroke and better quality of life than earlier designs and paracorporeal devices [3,4,13,14]. As the HeartMate 3 was designed for adults, its utilization is limited to patients weighing over 20 kg.

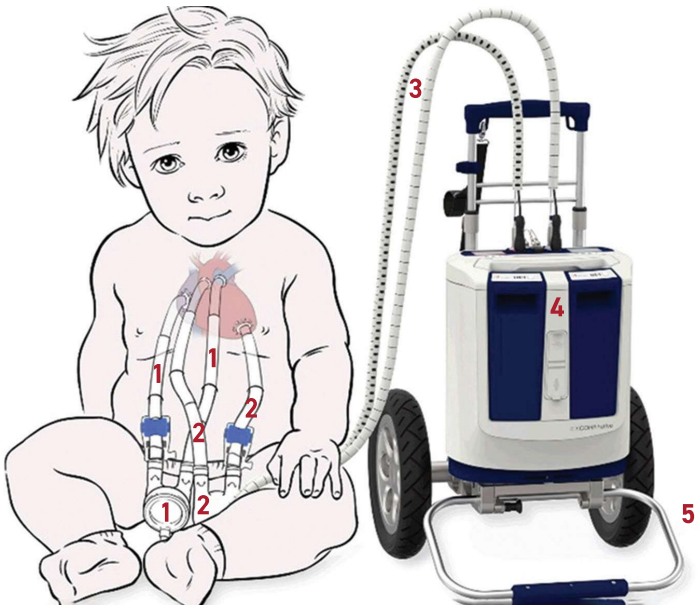
The devices were implanted at Schneider by a congenital cardiac surgeon aided by an adult cardiothoracic surgeon. A technician from Berlin Heart GmbH assisted with the initial device settings and connections. Patients with Berlin Heart remained hospitalized until transplantation, while patients with the HeartMate 3 were discharged to their homes. During the hospitalization, the patients were cared for by the multidisciplinary team that included pediatric intensivists, cardiologists, cardiac surgeons, physical therapists, speech and oral therapists, dietitians, and an educational team. The aim was early mobilization as well as psychological and educational support.

ANTICOAGULATION MANAGEMENT

As VADs hold a substantial risk of bleeding and thrombotic events, all patients were treated with anticoagulation, according to the commonly accepted guidelines, with frequent consultations with a senior pediatric hematologist [15]. Patients receiving HeartMate 3 were treated with anticoagulation and an antiplatelet agent, while patients with Berlin Heart received dual antiplatelet medications in addition to anticoagulation. The effectiveness of these medications was regularly evaluated by partial prothrombin time, VerifyNowTM, closure time, and platelet aggregation studies. Corticosteroid courses aimed to mitigate inflammatory episodes were selectively used as these have been reported to decrease stroke rates [16]. Unfractionated heparin or, more recently bivalirudin, were used as a primary anticoagulation until oral anticoagulants could be started [17].

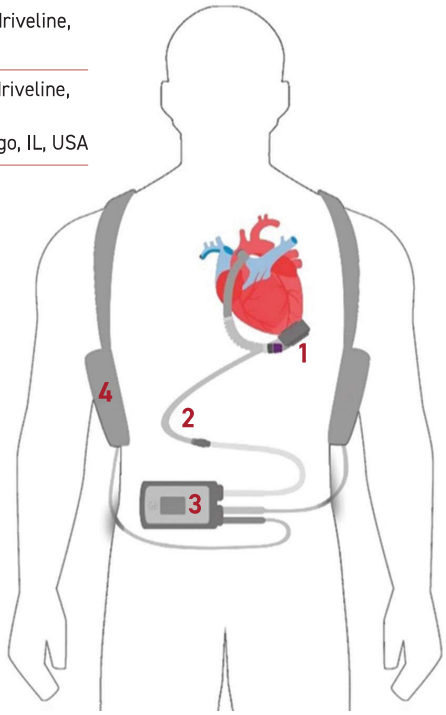
Figure 1. Diagram of Berlin Heart EXCOR® (Berlin Heart GmbH, Berlin, Germany) and the HeartMate 3™ (Abbott, Chicago, IL, USA) heart pumps
BiVAD = biventricular assist device, LVAD = left ventricular assist device

[A] Diagram of Berlin Heart cannulas, pumps (in biventricular support configuration), driving tubes, and console
1= RVAD cannulas and extracorporeal pump, 2 = LVAD cannulas and pump, 3 = driving tubes and flow sensors cables, 4 = EXCOR active driving unit, 5 = caddy
With permission from Berlin Heart GmbH, Berlin, Germany



[B] Diagram of HeartMate 3 pump, driveline, controller, and batteries

1 = intracorporeal LVAD pump, 2 = driveline, 3 = controller, 4 = batteries
With permission from Abbott, Chicago, IL, USA



RESULTS

PATIENT OUTCOMES AND DEVICE CHARACTERISTICS

Fifteen children underwent VAD implantation between October 2018 and May 2023. Nine (60%) of the patients were male. The median (interquartile range) age of implantation was 10.4 (3.9) years (range 2.5-16.6 years), and the median weight was 29 kg. The smallest patient weighed 11 kg. Indications for implantation were dilated cardiomyopathy of various causes, including idiopathic, genetic, chemotherapy-induced cardiomyopathy, Becker muscular dystrophy, and ischemic cardiomyopathy secondary to Kawasaki disease. In the last 5 years 79% of our heart transplant patients received VAD support prior to transplant.

Of the 15 implanted patients, eight (53.3%) were implanted with HeartMate 3 and seven (46.7%) received Berlin Heart devices. The choice to implant paracorporeal device was the need for biventricular support in three children and small patient size (11–15 kg) in four. The smallest patient to receive the HeartMate 3 weighed 21.6 kg and was 8 years old at implantation. Four patients were supported by extracorporeal membrane oxygenation (ECMO) prior to VAD implantation (26.7%), for 2–26 days [Table 2].

Two patients died while awaiting transplant. One succumbed to sepsis from persistent *Pseudomonas aeruginosa* bacteremia after one year on Berlin Heart BiVAD support. The other patient died of fatal intracranial hemorrhage 6 days following HeartMate 3 implantation. For all the patients, VAD was implanted as a bridge to transplant. Eleven patients received a heart transplant (73.3%), with a mean time to transplant of 221 days and a median time of 169 days (range 55–480 days). At the time of the submission of this article, two patients were currently supported with MCS, awaiting transplant.

ADVERSE EVENTS AND DEVICE-RELATED COMPLICATIONS

Four major bleeding events were observed in two patients, both of whom experienced central nervous system bleedings that led to death in one of them (mortality rate 13.3%, similar to other reports) [5]. The other patient also had a pulmonary hemorrhage and upper gastrointestinal bleeding. One patient suffered an ischemic stroke that led to paraplegia, which has since improved considerably. Five patients (33.3%) experienced nine events of major infections. These consisted of four

Table 2. Patient and device characteristics

Characteristic	Entire cohort	Berlin Heart*	HeartMate 3**
Implanted patients	15 (100%)	7 (46.7%)	8 (53.3%)
Median (range) age at device implantation, in years	10.4 (2.5–16.6)	7.0 (2.5–11)	11.5 (8–16.6)
Female sex	6 (40.0%)	4 (57.1%)	2 (25.0%)
Median body weight (range), kg	29.0 (11–57)	18.6 (11–44)	35.5 (21.6–57)
Diagnosis			
Dilated CMP	14 (93.3%)	7 (100%)	7 (87.5%)
Dilated CMP with NMD	1 (6.7%)	0	1 (12.5%)
Preimplant ECMO support	4 (26.7%)	4 (57.1%)	0
Support configuration			
LVAD support	12 (80.0%)	4 (57.1%)	8 (100%)
BiVAD support	3 (20.0%)	3 (42.9%)	0

*Berlin Heart EXCOR® (Berlin Heart GmbH, Berlin, Germany)
**HeartMate 3™ (Abbott, Chicago, IL, USA)
BiVAD = biventricular assist device, CMP = cardiomyopathy, ECMO = extracorporeal membrane oxygenation, LVAD = left ventricular assist device, NMD = neuromuscular disease
The numbers are presented as n (%) or median (range).

exit site infections, three events of bacteremia, one cytomegalovirus viremia, and one clostridium difficile infection. Three patients were successfully treated with a short course of systemic steroids due to fever and elevated inflammatory markers without an identified infection. Two patients had intestinal ischemia and bowel perforation that required colonic resection and an ileal stoma creation 5 and 9 days after the VAD implantation. Four Berlin Heart pump replacements were required in three patients due to clot formation. Another patient required pump replacement for upsizing due to his somatic growth. No events of pump malfunction or clotting were observed in HeartMate 3 implanted patients. Despite the high risk for adverse events and mortality, 12 of our patients (80%) had good neurologic outcomes [Table 3].

Table 3. Adverse events and mortality

Variable	Value
Mortality	2 (13.3%)
Bleeding	4 events in 2 patients (13.3%)
Central nervous system bleeding	2
Pulmonary hemorrhage	1
Gastrointestinal bleeding	1
Major Infections	9 events in 5 patients (33.3%)
Exit site infection	4
Bacteremia	3
Viremia	1
Other infection	1
Pump replacement	4 events in 3 patients (20.0%)
Ischemic stroke	1 (6.7%)
Inflammatory response	3 (20.0%)
Intestinal ischemia and perforation	2 (13.3%)

DISCUSSION

VADs play a critical and increasing role in supporting children with end-stage heart failure. Compared to temporary mechanical support such as ECMO, these devices have many advantages. Among them are stable cannula positioning, which enables weaning of mechanical ventilation, increased patient mobility and responsiveness to physical rehabilitation, fewer blood product transfusions, and lower incidence of infection and end-organ dysfunction [18]. The heart donation waitlist mortality has been shown to be much lower in pediatric patients with VAD than in children without bridge-to-transplant mechanical support [2]. Pediatric VADs have also demonstrated the capacity to reduce rates of renal and hepatic impairment, the reliance on parenteral nutrition, and the necessity for sedation, muscle-relaxants, inotropic support, and mechanical ventilation. These favorable outcomes have resulted in reduced hospital mortality following heart transplantation [19]. However, VAD implantation has only recently become an optional therapy for pediatric patients in Israel. Due to its novelty for children in our country and the low case volume, we suspect that many Israeli healthcare providers are unaware of the availability of this treatment modality.

The scarcity of heart donations is a global problem, and the shortage might be even more prominent in Israel. About one-third of pediatric heart transplant patients require VAD as a bridge to transplant [1,4,20]. Since the establishment our VAD program, only three patients received a heart transplant without being bridged by VAD. We suspect this disparity results from scarcity of pediatric heart donations and a long waiting list duration.

All our patients who required VAD were hospitalized and on continuous inotropic therapy, with severe signs of heart failure. Four patients were on ECMO support prior to VAD implantation. VAD implantation was used as a long-term rescue therapy while greatly improving quality of life. It enabled weaning from mechanical ventilation, inotropic support, and early mobilization. All the patients on HeartMate 3 were discharged, enabling them to return to school and to near-normal day-to-day activities. Discharging patients with the extracorporeal Berlin Heart device is not yet approved. Nevertheless, these patients can ambulate inside the hospital compound and its surroundings.

Studies have shown associations of late implantation of VAD with increased morbidity and mortality. These associations were particularly pronounced when the implantation followed the development of shock and end-organ damage [1,4]. The experience at our center was similar. Our first patient implanted with biventricular Berlin Heart after a prolonged ECMO run, never fully recovered and may have benefited from earlier MCS implantation. Although our cohort is too small for

statistical analysis, our results are consistent with previous data in which BiVAD support was shown as a risk factor for VAD mortality [1,8]. Thus, as our experience increased, we shifted to a more proactive approach, with the goal of avoiding implantation of a second VAD to support the right ventricle. This goal was achieved by aggressively treating pulmonary hypertension and optimizing right ventricular function prior, during, and after implantation. For this purpose, we used right ventricular afterload-reducing medication such as milrinone; pulmonary dilators such as sildenafil, nitric oxide, and inhaled iloprost; and inotropic support. We avoided the use of beta-blockers.

Fortunately, the need for VAD implantation in the pediatric population is extremely rare, and only a few children in Israel require VAD support each year. As the case volume is low, it may take time for a pediatric center to gain experience with VAD implantation and management. This experience and competency relate to surgical experience in the operating room but also with regard to devising protocols for patient selection, perioperative care, nursing protocols, and rehabilitation as well as providing ambulatory long-term follow-up. A multidisciplinary team of pediatric intensivists, noninvasive and invasive pediatric cardiologists, perfusionists, imaging specialists, and heart failure experts is of utmost importance in caring for these frail patients. Since the establishment of our VAD program, we have closely collaborated with the adult VAD program at Rabin Medical Center, which has vast experience in treating adults during and after VAD implantation. This collaboration has proven fruitful and successful in safely bringing most of our patients to heart transplantation.

CONCLUSIONS

We found that heightened institutional proficiency and extensive collaborative endeavors contributed to favorable outcomes of pediatric patients with heart failure. Given the constrained accessibility of pediatric cardiac donors in Israel, patients requiring heart transplants are compelled to endure prolonged waiting periods. Consequently, expedited referral of these patients to a VAD center for implantation assessment becomes imperative. Ideally, such evaluations should be conducted within a prominent pediatric transplant facility, characterized by extensive experience and utilization of strategies to preempt the necessity for ECMO or right ventricular assist device support. Timely VAD implantation in suitable candidates holds the potential to forestall further clinical deterioration, enhance quality of life, and curtail both mortality and morbidity rates.

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Capsule

SARS-CoV-2 viral persistence in lung alveolar macrophages is controlled by IFN-γ and NK cells

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA generally becomes undetectable in upper airways after a few days or weeks postinfection. **Huot** and colleagues used a model of viral infection in macaques to address whether SARS-CoV-2 persists in the body and which mechanisms regulate its persistence. Replication-competent virus was detected in bronchioalveolar lavage (BAL) macrophages beyond 6 months postinfection. Viral propagation in BAL macrophages occurred from cell to cell and was inhibited by interferon-γ (IFN-γ). IFN-γ production was strongest in BAL NKG2r+CD8+ T cells and NKG2Alo natural killer (NK) cells and was further increased in NKG2Alo NK cells after spike protein stimulation. However, IFN-γ production was impaired in NK cells from macaques with persisting virus. Moreover, IFN-γ also enhanced the expression of major histocompatibility complex (MHC)-E on BAL macrophages, possibly inhibiting NK cell-mediated killing. Macaques with less persisting virus mounted adaptive NK cells that escaped the MHC-E-dependent inhibition. These findings reveal an interplay between NK cells and macrophages that regulated SARS-CoV-2 persistence in macrophages and was mediated by IFN-γ.

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Capsule

Mortality in patients with psoriatic arthritis in Sweden: a nationwide, population-based cohort study

Exarchou and colleagues compared all-cause mortality and causes of death between patients with psoriatic arthritis (PsA) and the general population in Sweden. Adults with at least one main PsA diagnosis (International Classification of Diseases-10: L40.5/M07.0–M07.3) from outpatient rheumatology/internal medicine departments 2001–2017 were identified from the National Patient Register. All-cause mortality was elevated in PsA (hazard ratio [HR] 1.11, 95% confidence interval [95%CI] 1.07–1.16; incidence rate ratios [IRR] 1.18, 95%CI 1.13–1.22), mainly driven by increased risks in women (HR 1.23, 95%CI 1.16–1.30) and cases with longer time since diagnosis (HR 1.18 (95%CI 1.12–1.25). IRR of death were significantly increased for all ages except younger than 40 years, with the numerically highest point-estimates for ages 40–59 years. When adjusted for co-morbidity, however, the elevated mortality risk in PsA disappeared. Causes of death were similar among PsA cases/comparator-subjects, with cardiovascular disease and malignancy as the leading causes. The authors concluded that mortality risk in PsA in Sweden was about 10% higher than in the general population, driven by excess comorbidity and with increased risks mainly in women and patients with longer disease duration.

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