Pediatric mechanical circulatory support (MCS) has advanced tremendously over the last decade, with momentum building in the development and implantation of durable ventricular assist devices (VADs) in smaller children with increasingly complex anatomy. Despite these advancements, VAD support for children continues to lag behind support options for adults. The most obvious disparity is the limited number of devices suitable for children for both short- and long-term support. Thus, there has been burgeoning interest in developing devices specifically tailored to suit the unique needs of children. From a design perspective, pediatric VADs differ significantly from adult devices: they are required to support a wide range of patient sizes (from newborn to adolescence), to allow for the increased circulatory demand commensurate with growth, and to accommodate the anatomic and physiological heterogeneity of congenital heart disease. Beyond the challenges of designing and developing pediatric VADs, there are multiple barriers to the clinical evaluation of these devices because of the small number of children who require this level of support. Therefore, it is considered infeasible to test device safety and effectiveness through large randomized, controlled trials like the Randomized Evaluation of Mechanical Circulatory Support (REMATCH), a large adult study. Additionally, industry is disincentivized to invest the necessary resources in the research and development of pediatric-specific medical devices with applicability to such a narrow market population.

In the United States, the Food and Drug Administration (FDA) is tasked with the responsibility of ensuring that medical devices marketed in the United States have met the requirements establishing the safety and effectiveness for use in humans to treat a specific condition. Many pediatric-specific medical devices, including VADs, fall under the category of a humanitarian use device. Humanitarian use devices are devices that are used to treat or diagnose a rare disease (ie, end-stage heart failure) and applicable to a small subset of the population (ie, children). Acknowledging the critical unmet need to expand MCS options for children, the US FDA identified unique challenges to device development and enlisted the academic pediatric community, clinicians, Congress, and industry in a concerted effort to overcome these obstacles. This article discusses the advancements in VAD support for children, highlighting the US FDA orphan device program, current device options, the expansion of the application of VADs to challenging populations, and new device options for pediatric support on the horizon.

The US FDA Orphan Devices Program

Heart failure in children is a rare condition. The incidence of congenital heart disease in children is estimated at 8 per 1000 live births, and the incidence of cardiomyopathy is estimated at 0.58 per 100 000 children, with only a fraction of these children requiring MCS for end-stage heart failure. Therefore, although there is a critical need to support these extremely fragile patients, the small number of children and the high financial investment have deterred many industry sponsors from designing and evaluating circulatory support devices for children. Acknowledging the financial and logistical obstacles to device development for a small population, the US FDA Office of Orphan Products Development focuses on advancing the development and evaluation of products (devices, drugs, etc.) designed to treat rare diseases. A variety of programs exist, of which the Orphan Products Grant Program, the Humanitarian Use Device Designation program, and the Pediatric Device Consortia have played important roles in advancing MCS options for children. Developed in 1990 in response to the Safe Medical Devices Act, the Humanitarian Use Device Designation program provides an alternative pathway for market approval for devices intended to benefit patients of rare diseases that manifest in <4000 individuals in the United States per year. Devices that receive humanitarian use device designation may then be eligible for marketing approval under the humanitarian device exemption (HDE). An HDE application differs from other premarket applications in that, rather than demonstrate effectiveness, it needs to only demonstrate probably benefit in addition to safety.

To date, 2 pediatric VADs have been granted HDE approval in the United States. The MicroMed HeartAssist 5 (formerly the DeBakey VAD Child; MicroMed Technologies, Inc) was the first pediatric VAD granted HDE in 2004. This device was approved for use in children listed for heart transplantation who were 5 through 16 years of age with a body surface area of 0.7 to 1.5 m² and end-stage heart failure refractory to maximal medical management. At the time, this was the

From the Department of Cardiology, Children’s Hospital Boston, Boston, MA (C.J.V., E.D.B.); and Department of Cardiac Surgery, Children’s Hospital Boston and the Department of Pediatrics and Surgery, Harvard Medical School, Boston, MA (F.F.-T.).

Correspondence to Christina J. VanderPluym, Department of Cardiology, Boston Children’s Hospital, 300 Longwood Ave, Boston, MA 02115. E-mail Christina.vanderpluym@childrens.harvard.edu

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only intracorporeal (fully implantable) VAD modified for use in children. Because of the device size and multiple reports of neurovascular events related to thromboembolism, the device was not widely used after HDE approval. The second device to receive HDE approval was the Berlin Heart EXCOR (Berlin Heart, Inc, Berlin, Germany) in December 2011 (Figure 1). The prospective multi-institutional investigational device exemption trial compared patients with the Berlin Heart EXCOR with a propensity-score matched historical control group supported on extracorporeal membrane oxygenation (ECMO). Between May 2009 and December 2010, a total of 48 patients ≤16 years of age met the inclusion criteria and were separated into 2 cohorts according to body surface area (cohort 1, <0.7 m²; cohort 2, ≥0.7 m²) with 24 patients in each group. The median survival time for cohorts 1 and 2 (>174 and 144 days, respectively) far exceeded that of ECMO (cohort 1, 13 days; cohort 2, 10 days; P<0.001 by log-rank test). Serious adverse events occurred in the majority of patients and included bleeding, infection, and stroke, with a notable 29% rate of stroke in both VAD cohorts. Based on the results of the investigational device exemption trial, the Berlin Heart EXCOR was granted HDE approval as a device to provide long-term MCS as a bridge to cardiac transplantation in children with severe left or biventricular dysfunction.

The Berlin Heart investigational device exemption trial proved to be an important milestone in advancing the field of MCS for children in the United States. Not only did the trial result in successful US FDA approval of the device, but it also brought to light the important challenges of advancing the field of pediatric VAD support. First, the trial illustrated the lack of durable device options for children. Although the Berlin Heart is vastly superior to ECMO in terms of long-term survival, the device still carries a significant risk of adverse events, namely cerebrovascular events with a rate of 29%. The US FDA acknowledged the need for further investigation into the neurological sequelae of the Berlin Heart, and the medical community universally agreed that MCS-related morbidity was unacceptably high with the currently available device technology. Second, during trial design and execution, it became apparent that there had been a paucity of formal definitions of adverse events in pediatric MCS. The pediatric VAD community drew on the experience of its adult VAD colleagues in defining adverse events, with important pediatric specific modifications. Most notable was the challenge of assessing and defining neurological dysfunction secondary to cerebrovascular events in children. There is no universally accepted method of objectively evaluating and quantifying neurological dysfunction that can be applied to the entire age range from neonate to adolescent. This issue remains unresolved, with a dedicated effort underway to standardize the way we evaluate device performance and outcomes in children. To this end, the academic community, industry, and the US FDA foresaw the need for a pediatric-specific VAD database, and Pedimacs came to fruition in 2012. Working in parallel with the adult VAD database (Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS]), Pedimacs was developed to serve as a comprehensive registry with global participation and pediatric-specific inclusion criteria, data elements, and adverse events. The goals of this registry are to better characterize device performance as used in a broader population, to optimize patient outcomes and to refine patient selection for VAD therapies, to develop “best practices” by analyzing outcomes and adverse events, and to

Figure 1. Berlin Heart EXCOR (Berlin Heart, Inc, Berlin, Germany).
facilitate and guide the development and clinical evaluation of the next generation of devices.

**Current VAD Options for Children in the United States**

Currently, the Berlin Heart EXCOR VAD is the only HDE device approved by the US FDA with widespread use in the United States. However, several other MCS devices are being used in children with increasing frequency through other regulatory pathways. The US FDA permits VAD implantation in children under the following pathways: off-label use of an otherwise FDA-approved adult device, compassionate use of investigational adult devices, emergency use of investigational devices on a case-by-case basis, and use of a device fabricated from US FDA–approved components (eg, ECMO circuits).6 Once medical devices are approved for use in adults, they can be considered for use in children depending on how the device is “labeled” (ie, whether there is a specific weight, size, or age restriction listed for the device). Currently approved VADs in adults have no restriction specifically outlined for age or size; hence, they can be used in children. Off-label use of medical devices is a common occurrence in the field of pediatric MCS. It entails the use of a device outside the population or purpose for which the safety and effectiveness profile of the device was originally evaluated. For short-term support (temporary MCS), the following devices have been used in children: the TandemHeart (Cardiac Assist, Inc, Pittsburgh, PA) percutaneous VAD,7 the Rotaflow (MAQUET Medical Systems, Wayne, NJ), the CentriMag (Thoratec Corp, Pleasanton, MA),8,9 and the Abiomed Impella 2.5/5.0 (Abiomed Inc, Danvers, MA).10,11 For long-term support (durable MCS), the following devices have been used primarily in larger children and adolescents: the HeartMate II (Thoratec Laboratories Corp, Pleasanton, CA),12–15 the HeartWare HVAD (HeartWare Inc, Framingham, MA)16–18 (Figure 2), and the Syncardia Total Artificial Heart (Syncardia Systems, Inc, Tuscon, AZ)19,20 (Figure 3 and the Table) Off-label use plays a pivotal role in expanding MCS options for children. However, it is important to realize that the safety and effectiveness of these devices have not been studied in a rigorous, prospective manner in the given population. Children differ greatly from adults, not only in size but also in anatomic, physiological, and molecular aspects. Without prospective evaluation, these differences may result in unanticipated outcomes and adverse events not originally encountered in the adult population. Therefore, although off-label use will be a continued practice of pediatric medicine, it is the responsibility of industry and clinicians to
vigilantly adjudicate and report adverse events to ensure that there is continual critical evaluation of safety profiles for this emerging technology in children.

### Expanding VAD Support to Challenging Pediatric Populations

#### Single-Ventricle Anatomy and VAD Support

Improvement in preoperative, perioperative, and postoperative management of patients with congenital heart disease has resulted in a dramatic increase in long-term survival. Life expectancy for children with most types of congenital heart lesions is now comparable to that of the general population. However, there is a subset of congenital heart disease, namely single-ventricle anatomy, in which long-term mortality and morbidity into adulthood remain unacceptably high. According to data from the Pediatric Heart Transplant Study (PHTS) and Cardiac Transplant Research Database, the most common structural cardiac lesion from 6 months of age to adulthood necessitating heart transplant is single-ventricle anatomy.21 This growing population of failed single-ventricle palliations will benefit from effective MCS as a bridge to transplantation or even destination therapy (DT). To date, however, this has been a disappointing endeavor, with higher mortality and morbidity reported in a variety of single-center experiences.

The unnatural history of Fontan (total cavopulmonary connection) circulation is that of progressive systemic venous congestion with the sequelae of protein-losing enteropathy and renal, hepatic, and intestinal congestion. The pathways of deterioration may vary and include systemic systolic ventricular dysfunction with low cardiac output and elevated left atrial pressures, diastolic ventricular dysfunction with elevated ventricular end-diastolic pressures resulting in elevated Fontan pressures, or high transpulmonary gradient with systemic venous hypertension and congestion. Pure systolic ventricular dysfunction can be managed successfully with implantation of a VAD. In situations of diastolic dysfunction or restrictive physiology, in addition to decreased systolic function, a continuous-flow pump may be superior by providing continuous unloading of the pulmonary venous system.22 The last route of failure, classically denoted as failing Fontan physiology, is the least remediable by currently available VADs and ultimately necessitates pump support within the Fontan pathway by a Fontan assist device or a cavopulmonary assist device. There have been multiple attempts and continued development of an assist device for the cavopulmonary connection.23–26 An ideal Fontan assist device/cavopulmonary assist device would provide equal continuous flow at a low-pressure head to avoid lung perfusion injury, would be resilient to afterload to overcome elevated and possibly fluctuating pulmonary vascular resistance, and would avoid inlet suction within the Fontan pathway in the absence of a venous reservoir. Rodefeld et al27 have developed a pediatric transcatheter-expandable impeller pump that is positioned at the crux of the cavopulmonary junction and directs flow into both lungs. Although this device is still far from clinical application, significant strides have been made in understanding the unique anatomic and physiological constraints of total cavopulmonary connection circulation, with the hope of a durable assist device on the horizon.

In the meantime, options to unload the systemic venous system in failed Fontan circulation include revision of the Fontan pathway with the creation of a larger systemic venous capacitance chamber and insertion of cannula to an extracorporeal device (Berlin Heart EXCOR or centrifugal pump) or

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**Table. Ventricular Assist Devices Used in Children and Adolescents**

<table>
<thead>
<tr>
<th>Device</th>
<th>Size Restrictions</th>
<th>Duration of Support</th>
<th>Type of Support</th>
<th>Pump Flow</th>
<th>Approved for Use by US FDA</th>
<th>Pathway of US FDA Approval</th>
<th>Labeled Excluding Use in Children</th>
<th>Studied Prospectively in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary ECMO</td>
<td>None</td>
<td>days</td>
<td>Biventricular</td>
<td>Continuous</td>
<td>Yes</td>
<td>510K</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CentriMag</td>
<td>None</td>
<td>Days–weeks</td>
<td>Univentricular or biventricular</td>
<td>Continuous</td>
<td>Yes</td>
<td>510K</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rotaflow</td>
<td>None</td>
<td>Days–weeks</td>
<td>Univentricular or biventricular</td>
<td>Continuous</td>
<td>Yes</td>
<td>510K</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>TandemHeart pVAD</td>
<td>N/A</td>
<td>Days</td>
<td>Univentricular</td>
<td>Continuous</td>
<td>Yes</td>
<td>510K</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Impella 2.5/5.0</td>
<td>N/A</td>
<td>Days</td>
<td>Univentricular</td>
<td>Continuous</td>
<td>Yes</td>
<td>510K</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Durable Berlin Heart</td>
<td>Wt &gt;3 kg</td>
<td>Months–Years</td>
<td>Univentricular or biventricular</td>
<td>Pulsatile</td>
<td>Yes</td>
<td>HDE</td>
<td>Labeled for children</td>
<td>Yes</td>
</tr>
<tr>
<td>HeartWare</td>
<td>Wt =15 kg</td>
<td>Years</td>
<td>Univentricular or biventricular</td>
<td>Continuous</td>
<td>Yes</td>
<td>PMA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>HVAD</td>
<td>Wt &gt;30 kg</td>
<td>Years</td>
<td>Univentricular</td>
<td>Continuous</td>
<td>Yes</td>
<td>PMA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>HeartMate II</td>
<td>BSA &gt;1.7 m²</td>
<td>Years</td>
<td>Biventricular</td>
<td>Pulsatile</td>
<td>Yes</td>
<td>PMA</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

BSA indicates body surface area; ECMO, extracorporeal membrane oxygenation; FDA, Food and Drug Administration; 510K, pathway of approval based on demonstrating equivalence to predicate device; HDE, humanitarian device exemption; HVAD, PMA, postmarket approval; pVAD, percutaneous ventricular device; and Wt, weight.
takedown of the Fontan back to Glenn (bidirectional cavopulmonary anastomosis) and implantation of systemic VAD. The latter option provides better unloading of the infradiaphragmatic circulation at the cost of lower oxygen saturations and risk of paradoxical emboli. It is also thought that a systemic VAD in patients with preserved systolic function but elevated end-diastolic pressures and consequently pulmonary venous congestion may be beneficial in lowering left atrial pressures and alleviating symptoms of Fontan failure. Even a marginal decrease in left atrial pressures may be sufficient to decrease Fontan pressures and to improve systemic venous congestion. As device technology improves, with a lower adverse event profile and better compatibility with activities of daily living, VADs may soon prove to be adjunctive therapy in protein-losing enteropathy refractory to maximal medical therapy.

Posttransplantation Graft Failure and VAD Support
Cardiac graft failure can manifest either early (<30 days) or late after transplantation as a result of variable causes. Current strategies to increase the donor pool, including the use of marginal donors and desensitization with an HLA-incompatible donor, may be increasing the risk of posttransplantation graft failure.

ECMO has been the mainstay of MCS strategies for graft dysfunction, providing complete respiratory and cardiac support and allowing recovery or preservation of end-organ function. However, ECMO is limited in its duration of support to weeks and is fraught with bleeding, thrombotic, and infectious complications that increase exponentially over time. Therefore, intermediate- to long-term MCS strategies have been attempted with guarded success. The challenges of MCS in graft failure are multifaceted and include redo sternotomy, increased risk of infection, and poor wound healing in the setting of continued immunosuppression, progressive biventricular dysfunction with polyvalvar involvement, and arrhythmia. Thus, standard LVAD support is generally not successful, with most patients requiring biventricular support. Therefore, many have felt that total extraction of the graft with implantation of a total artificial heart, the Syncardia Total Artificial Heart (Syncardia Systems, Inc, Tucson, AZ; Figure 2), may be an advantageous support strategy because it obviates the need for continued immunosuppression. Currently, the Total Artificial Heart is not applicable for use in most children because the two 70 ml pneumatically driven pumps for right and left heart support require a minimum anterior-posterior chest diameter of 10 cm at the level of thoracic vertebra 10 (T10) to fit. However, a 50 ml Syncardia Total Artificial Heart pump has been developed with a lower size range of 1-m² body surface area that may have a wider applicability to the pediatric population.

There remains equipoise about the optimal device strategy for circulatory support for graft failure, be it ECMO or VAD. The cause of graft failure and prognosticated recovery should be taken into consideration when planning the optimal modality for MCS. Venoarterial ECMO should be reserved for donor-related graft dysfunction (eg, prolonged donor ischemic time) expected to recover within 1 to 2 weeks, whereas hyperacute rejection or profound graft vasculopathy requires long-term VAD options, of which the Syncardia is the only intracorporeal device to provide biventricular support and to allow discontinuation of immunosuppression and its associated complications.

VADs as DT in Children
DT is the use of a VAD as a primary therapeutic option when heart transplantation is contraindicated or not desired. The landmark REMATCH trial in adults demonstrated that the implantation of LVADs for DT was superior to standard medical therapy in patients with end-stage heart failure who were not eligible for transplantation. Now, more than a decade after this trial, the use of VADs as DT in adults is an accepted therapy to improve quality of life.

From the success of DT in adults, it is not surprising that this indication is now being more widely considered for children. However, the ability to offer DT remains restricted to children who are large enough to use the currently available intracorporeal devices suitable for outpatient care. Patient selection for this type of therapy is of paramount importance and likely an evolving process. Children who may benefit from DT include those with Duchenne muscular dystrophy with cardiomyopathy, children with chemotoxicity-induced cardiomyopathy with ongoing malignancy or unlikely long-term remission, those with complex palliated congenital heart disease with multiple comorbidities, those with retransplantation for this type of therapy to improve quality of life for the patient and family. Quality of life is a subjective and relative term that denotes the degree to which an individual enjoys the possibilities of his or her life. This can be defined only by the patient and family. Having a clear understanding of the patient’s current quality of life and how a VAD may or may not improve that quality of life will help clarify patient selection and post-VAD management. Additionally, the criteria for elective VAD discontinuation in both futile and nonfutile situations need to be agreed on before device implantation and reviewed frequently during device support. Ensuring that these discussions occur early in the course of disease allows the child or adolescent to have an active role in the decision making for both VAD implantation and criteria for VAD deactivation.

The use of VADs for DT in children will continue to evolve as device technology improves, narrowing the gap between quality of life and survival outcomes for VADs and heart transplantation. Commensurate with the advancement in device technology, we, as a field in pediatric advanced
cardiac therapies, need to keep pace with the ethical implications and clinical challenges of altering the natural history of life-limiting conditions by acknowledging the benefits and critically evaluating the consequences.

Expanding Device Options for Children

Although options for durable VAD support continue to increase for larger children and adolescents, infants and small children remain restricted to the Berlin Heart EXCOR. Almond et al demonstrated that pediatric heart transplantation wait list mortality is substantially higher in the smallest children, the very children with the fewest VAD options. In light of the need for improved device options for the smallest patients, the National Heart, Lung, and Blood Institute of the US National Institutes of Health embarked on a multimillion-dollar initiative to develop pediatric-specific MCS options. The planned National Heart, Lung, and Blood Institute–sponsored trial called Pumps for Kids, Infants and Neonates (PumpKin) will evaluate the Infant Jarvik (Jarvik Heart Inc, New York, NY) VAD (Figure 4) randomized to the Berlin Heart EXCOR in infants and small children. The Infant Jarvik is an intracorporeal continuous-flow device intended for univentricular support in children 3 to 15 kg. The PumpKin trial will also evaluate an ECMO device (Levitronix PediPl, Levitronix LLC, Waltham, MA) specifically designed for infant support. This trend toward the development and application of continuous-flow devices for children echoes the paradigm shift of adult VAD support from pulsatile- to continuous-flow VADs.

The CircuLite Synergy Pocket Micro-Pump (CircuLite, Saddle Brook, NJ; Figure 5) is currently one of the smallest VADs in clinical trial. The pump is the size of an AA battery and can be implanted off cardiopulmonary bypass through a right-sided minithoracotomy procedure. The device is intended to provide partial left heart support with an inflow cannula in the left atrium and outflow graft to the right subclavian artery, providing flows of \( \approx 3 \) L/min. Currently, the micropump has CE marking approval in Europe and FDA conditional approval in the United States to begin enrolling eligible patients in an investigational device exemption feasibility trial. The Safety Evaluation of the CircuLite SYNERGY Circulatory Assist Device in a Non-Inotrope Dependent, Ambulatory Patient With End-Stage Chronic Heart Failure: A Pilot Study (IMPACT) will enroll 20 adult patients at 7 US centers. Although the CircuLite Synergy was
initially developed for use in adults, its small size and low flow make the device particularly well suited for implantation in children. In 2009, CircuLite Inc was awarded a Fast-Track Phase I-II Small Business Innovation Research grant from the National Institutes of Health to fund the development of a pediatric circulatory assist device based on the Synergy Pocket Micro-Pump design. Most recently, in July 2013, the US Department of Health and Human Services awarded a federal grant to CircuLite Inc as part of the Department of Health and Human Services Small Business Innovative Research Program to fund the development of a system that will support infants and young children awaiting heart transplantation. It is encouraging that both government and industry are now devoting efforts to expanding the armamentarium of MCS options for the smallest and most fragile patients.

Conclusions

MCS for infants and children has evolved from purely a heroic endeavor to an established therapy of end-stage heart failure. There is mounting interest in addressing the challenges of advancing MCS options in children by academic, government, and industry leaders. Continued clinical experience with VADs in smaller children with variable cardiac anatomy will no doubt improve outcomes over time, driving new device technology to the forefront of clinical practice. Through standardization of adverse event definitions and evaluation of quality of life with VAD support, we will gain vital information on optimizing device performance and technology in future generations of pediatric devices.

Disclosures

None.

References


Key Words: child ◼ compassionate use trials ◼ heart-assist devices ◼ pediatrics
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Christina J. VanderPluym, Francis Fynn-Thompson and Elizabeth D. Blume

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