Curr Pediatr Rep (2015) 3:245–254
DOI 10.1007/s40124-015-0085-9

Children Are Not Small Adults: Options for Pediatric Ventricular Assist Devices

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Published online: 4 August 2015

Abstract The number of children supported with ventricular assist devices (VADs) has grown rapidly over the last few years. VAD use in children holds the promise of improving the outcomes in pediatric end-stage heart failure; however, the risk–benefit profile inherent to VAD use is not uniform across all ages, sizes, and diagnoses. Device use in children has underscored a number of issues that distinguish pediatric and adult heart failure such as the high prevalence of complex congenital heart disease and the challenges inherent to supporting infants and small children. The use of VADs in children also raises a range of social, emotional, and logistic changes unique to children across the age spectrum.

Keywords Pediatric cardiology · Ventricular assist device · Heart failure

Introduction

The population of children with end-stage heart failure is growing. Advanced imaging techniques have lead to improved recognition of myocardial disease. In addition, there has been a rise in the number of patients with congenital heart disease who are surviving early childhood but are later suffering from failed palliation, in spite of advances in surgical technique and improved early outcomes [1, 2]. Although very different than adult heart disease, care paradigms for these pediatric patient populations have been adapted from adult heart failure guidelines. As we extrapolate adult data and mold adult care models to fit the care of children, pediatric and adult practices diverge when we consider mechanical support options. While adult-sized patients have various options for mechanical support, the small child who has failed medical management has limited options due to size or anatomic limitations.

Fortunately, the field is changing rapidly. The first pediatric-specific device, the Berlin EXCOR, was approved by the FDA in 2011. In addition, PediMACS, a NIH-funded registry, started to collect data on pediatric device patients in 2012, allowing for multi-center collaborations to improve patient outcomes. Aided by virtual surgery and increasing experience, pediatric care teams are using second and third generation adult devices in smaller children. This evolution in the approach to pediatric support is allowing for children to be discharged back into their communities to await organ transplantation or, in select cases, allowed children who are not eligible for transplantation to be on "chronic support."

Patient Selection and Timing of Implantaion

One of the most critical, yet most difficult, decisions to be made by a mechanical circulatory support team is the timing of device placement. Among adults, the improvement in clinical outcomes [3] using continuous flow ventricular assist devices (VADs) has prompted earlier device

This article is part of the Topical Collection on *Cardiology*.

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placement. While there has been a trend towards earlier use, the debate about when to initiate mechanical circulatory support remains a point of contention in adult care. This is underscored by the initiation and subsequent suspension of the Randomized Evaluation of VAD InterVEntion Before Inotropic Therapy (REVIVE-IT) trial, which compared VAD to optimal medical management in ambulatory patients with moderate heart failure. The question remains even more of a conundrum in pediatrics given the paucity of literature, the variations in patient size, patient anatomy and the limited number of devices FDA approved for support, especially in the smallest patients. Thus, there is significant practice variation within the field and the timing of when to place a child on support remains as much of an art as a science with much of the "optimal timing" extrapolated from adult data.

In general, the use of mechanical support is indicated when medical therapy has failed. The phrase "when medical therapy has failed" can be interpreted many different ways and is dependent on the experience of the program. In adults, patients who are Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) stage I (cardiogenic shock) and 2 (progressive decline on inotropic support) have been shown to have worse outcomes post-VAD placement [4, 5•] than those implanted earlier in the disease process (stable on inotropes). It has also been shown repeatedly that adults who already have end-organ dysfunction when undergoing device placement have an increase in mortality [5•, 6–7]. In pediatrics, similar results were shown in the Berlin Heart EXCOR trial, as patients with pre-implant renal dysfunction or increased bilirubin had significantly worse outcomes [8•] when compared to those who did not. Despite the data supporting earlier implantation, implantation in cases of cardiogenic shock remains common, if not the rule, in pediatrics. Data from EXCOR trial database showed 44 % of patients were INTERMACS profile 1 [9•] and a slightly higher percentage (57 %) in the compassionate use cohort [8•]. Furthermore, 27 % of the patients from the EXCOR investigational device exemption (IDE) study cohort [9•] and 48 % of the compassionate use cohort had undergone pre-implant ECMO [8•]. While the optimal timing of implantation remains debatable, it is clear that increasing center experience may fundamentally alter the clinical choices and outcomes as a mechanical support team matures [10]. Currently, our institution begins evaluating patients who require one inotrope and have some evidence of end-organ dysfunction (we include feeding intolerance or the inability to wean from the ventilator in this group). Given that many centers are only starting to gain experience with VAD implantation, it will be interesting to monitor the evolution in implantation trends as centers gain more experience and as more advanced/durable devices become available.

Fortunately, absolute contraindications to the use of VADS in pediatrics are rare. Irreversible end-organ dysfunction has historically been a contraindication but with more experience we have determined that "irreversible end-organ dysfunction" is hard to predict and with an increase in cardiac output end-organ failure may be recoverable [7], even when severe [11]. Furthermore, the use of short-term mechanical circulatory support may allow for end-organ recovery and patient optimization prior to long-term VAD placement [12, 13]. The increase in programs offering dual organ transplantation may also lead to increased leniency in VAD placement in patients who are dialysis dependent and may improve post-transplant outcomes compared to heart transplant alone in patients with marginal renal function [14].

Other relative contraindications may include active infection and a hematologic disorder that prevents anticoagulation. Similar to transplantation, chromosomal abnormalities should not be a contraindication to mechanical support unless there are additional physical abnormalities that would hinder patient care and ultimately survival.

Cardiac specific contraindications to device therapy are also rare. Device use was originally focused on patients with large ventricles (dilated cardiomyopathy) due to concerns that small ventricular size may obstruct the ventricular cannula. Recent evidence suggests that successful implantation is possible in patients with smaller ventricular volumes as occurs in patients with restrictive or hypertrophic cardiomyopathy. Both myocardial abnormalities may impede filling into the ventricular inflow cannula and at times may require an atrial cannulation. Despite these modifications, acceptable results may be possible [15, 16]. These results are notable for pediatric patients for a couple of reasons. First, this may provide a therapeutic option for pediatric patients with hypertrophic cardiomyopathy or restrictive cardiomyopathy who lack medical therapy options and suffer from poor long-term outcomes [17, 18]. Second, these results suggest reasonable outcomes may be possible in patients with smaller left ventricular volumes. This becomes more and more relevant as we use third generation devices in smaller children.

Device Choice

Although using device therapy as a bridge to transplantation is the most common indication, children with a potentially recoverable process such as myocarditis, post-cardiotomy myocardial dysfunction, or post-arrest cardiac dysfunction are commonly encountered. Although often difficult to determine, the possibility of recovery and the intent of the "bridge" must be factored into the choice of

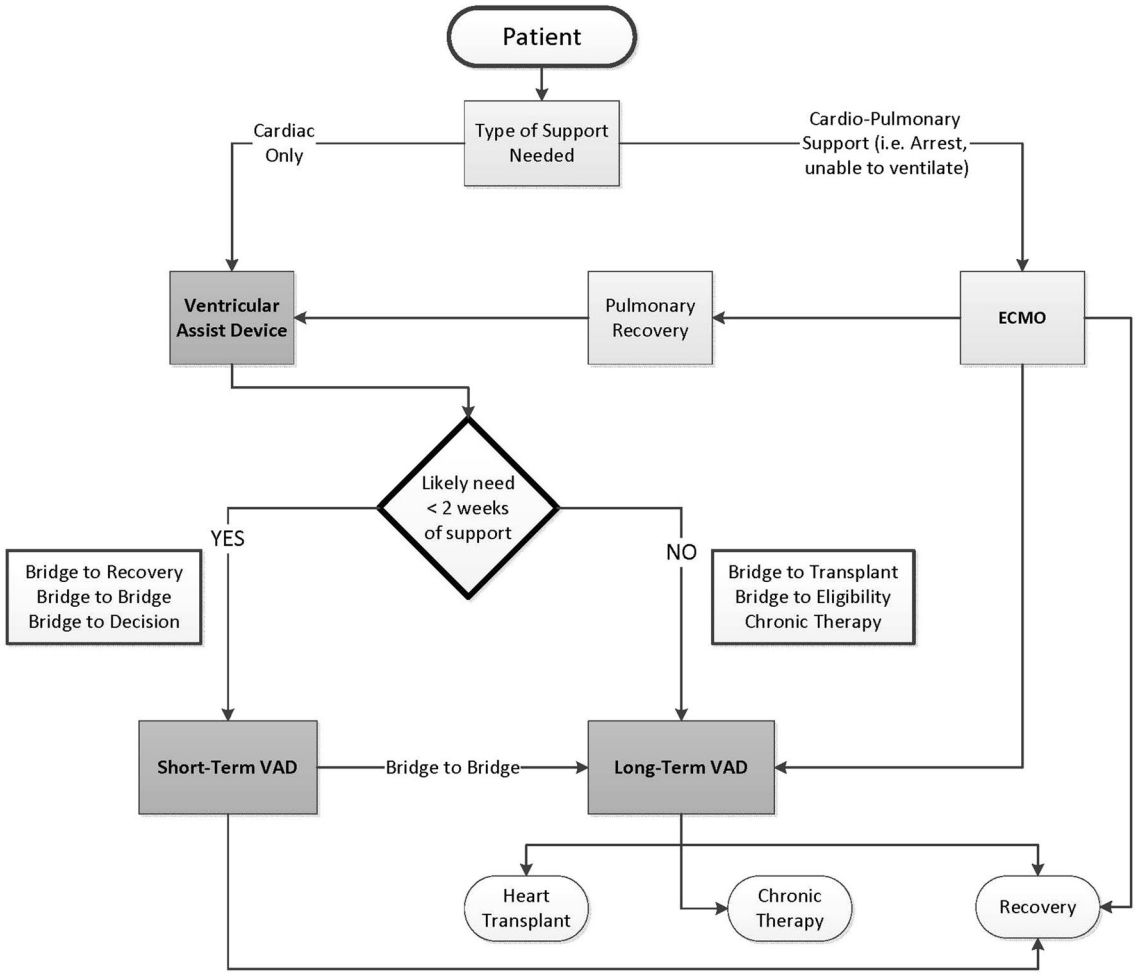

Fig. 1 Recommendations for device selection

what device to use for support. At our institution, we divide our device selections into short- and long-term support options (Fig. 1). We define short term as devices that will be used for approximately 2 weeks, this time frame is based on ECMO data that has shown an increase in the occurrence of complications after 2 weeks. If recovery does not appear to be an option a more durable long-term device will be chosen. Short-term device support may also allow time for end-organ recovery or patient optimization prior to long-term VAD placement (so-called "bridge to a bridge") [13]. The time afforded by short-term VAD support will also allow the mechanical circulatory support team time to initiate a full transplant evaluation as transplant candidacy continues to play an integral role in device choice in pediatric patients. Over the long-term, given the scarcity of organs, durability of the current devices and development of miniaturized devices, pediatric chronic therapy may become more common, but at the moment transplantation remains the rule.

Short-Term Devices

Short-term ventricular assist devices provide a mechanism to support patients with cardiogenic shock or as a means of temporary support following potentially reversible cardiac dysfunction (i.e., myocarditis, post-cardiotomy cardiac dysfunction). Some adult centers have advocated the use of these devices in cases of refractory cardiogenic shock as a "bridge to decision" [13] given the suboptimal outcomes associated with placement of durable devices in cases of cardiogenic shock [4, 19]. As a referral center, one may also receive transfers of very ill patients who are not well known to your institution but who clearly need support. Implantation of a short-term device can be done off cardiopulmonary bypass allowing time for a new team to assess a patient's etiology of heart failure and their candidacy for transplantation or chronic VAD therapy. There is limited pediatric experience with short-term devices [20, 21•], though anecdotal experience suggest the use is

Table 1 Short-term devices

Device (manufacturer)	Placement	Pump type	Patient size recommendations	Flow range (L/min)
RotaFlow® (Maquet, Rastatt, Germany)	Central cannulation	Centrifugal	No minimum	<10
PediMag® (Thoratec, Pleasanton, CA, USA)	Central cannulation	Centrifugal	<20 kg	<1.5
CentriMag® (Thoratec Pleasanton, CA, USA)	Central cannulation	Centrifugal	>20 kg	<10
Tandem Heart® (Cardiac Assist, Pittsburgh, PA, USA)	Percutaneous	Centrifugal	BSA >1.3 m^2	<5
Impella® 2.5/5.0 (Abiomed, Danvers, MA, USA)	Percutaneous	Axial	BSA >1.3 m^{2a}	<2.5; <5

[a] A left ventricular long axis dimension of 7–11 cm, depending on the device, it also recommended by the manufacturer

growing. As the field becomes more familiar with using short-term devices, an increase in the use of devices such as the PediMag may be seen in populations (i.e., children <10 kg) that have been deemed high risk for Berlin Heart implantation. The most commonly used short-term ventricular assist devices are extracorporeal centrifugal pumps, these devices are able to support patients across the age/size spectrum (see Table 1). Percutaneously placed devices are also available, though anatomic limitations have greatly limited their use in pediatrics.

Long-Term Devices

For patients who have a low likelihood of recovery, a long-term device will support them to transplantation or as chronic support if desired (Fig. 2).

Pulsatile Devices

The development of VADs capable of supporting pediatric patients has dramatically altered the landscape of pediatric heart failure and transplantation. Early, predominantly single-center studies provided the first evidence that pulsatile VADs could be used to bridge pediatric patients of all sizes to transplant [22–27]. The results of these studies also suggested pulsatile VADs could provide significant morbidity and mortality advantages compared to ECMO. These data became the basis for the first randomized pediatric ventricular assist trial [28] using the Berlin Heart® EXCOR (Berlin Heart, The Woodlands, Texas). The results of the investigational device exemption (IDE) study led the FDA to approve the device for bridge to transplantation in children in December 2011. The initial report and the subsequent analyses of the IDE database comprise the largest and most comprehensive pediatric VAD experience to date, and thus will form the focus of this section.

The IDE trial cohort, which included 48 patients, showed patients bridged to transplant on the EXCOR had significantly higher survival rates (88–92 % bridged to transplant or recovery) compared to historical ECMO controls (67–75 % bridged to transplant or recovery) [9•]. Subsequent analysis of the 204 patients from the IDE study (IDE trial cohort plus the compassionate use cohort) [8•] identified risk factors for increased mortality including end-organ dysfunction, small patient size, and use of biventricular support. Neurologic insult was the leading cause of death and thromboembolic strokes were more than twice as common as hemorrhagic strokes. While the percentage of patients suffering a neurologic event in the EXCOR study is significantly higher than those reported with newer continuous flow VADs [29, 30], the event rate is similar to the event rate reported with early studies using pulsatile devices in adults [31]. The extent and timing of neurologic insults were cataloged in a subsequent analysis [32•]. Unfortunately, the study was unable to reliably identify patients at risk for stroke based on pre-implant characteristics.

An additional pulsatile device, the total artificial heart (TAH-t) (SynCardia Systems Inc., Tuscon, AZ, USA), has been used to bridge a small number of pediatric patients to transplant. Indications include: patients with heart failure and left ventricular thrombus [33], biventricular heart failure [34, 35], allograft failure following heart transplantation [36•], congenitally corrected transposition with failing systemic ventricle [37], restrictive disease, and end-stage failing Fontan [38]. Use of the device has been limited in children due to the large footprint of the 70 cc device. The development of a 50 cc device and the use of virtual implantation [39•] may expand the use of the TAH-t in the future. The 50 cc TAH-t is currently available in the United States for compassionate use. The proposed device study will be only the second device study that will enroll pediatric patients. There will be a pediatric study arm, and both a pediatric and adult compassionate use arm. Conceptually, children as young as 10 years of age and with a BSA as low as 1.2 m^2 will benefit from the smaller footprint.

Continuous Flow Devices

While pediatric VAD use has been dominated by the Berlin EXCOR, the new era has brought a variety of different

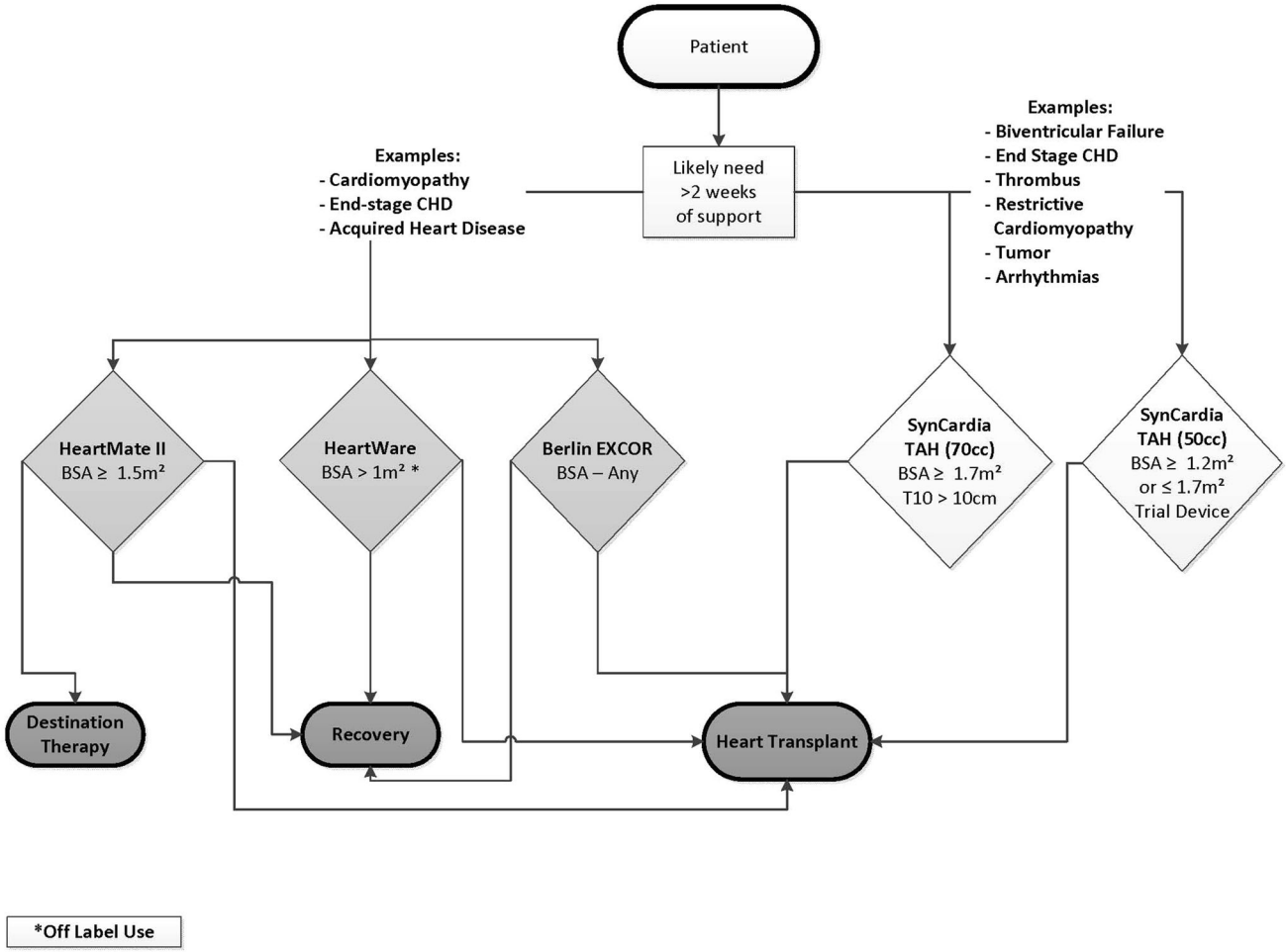

Fig. 2 Recommendations for long-term device selection

devices. Pediatric VAD utilization is beginning to follow the adult trend, as continuous flow devices are increasingly used in pediatrics, especially in teenagers. Continuous flow VADs have been the dominant VAD technology among adults since the Heartmate II® (Thoratec, Pleasanton, CA, USA) was approved for bridge to transplant in 2008. Continuous flow VADs have accounted for 100 % of the devices implanted for destination therapy since the Heartmate II® was approved for destination therapy in 2010 [40]. The pediatric experience with continuous flow VADs, while limited, is growing. In 2012, only one independent pediatric center was implanting second and third generation devices and now greater than 15 pediatrics centers are using these devices. The feasibility of implantation of continuous flow VADs in children has been demonstrated in case reports and case series [41–46]. The largest published experience to date was a retrospective analysis of all pediatric patients (26 children) who received a Heartmate II between April 2008 and September 2011 [47•]. Cabrera et al. compared the outcomes among the pediatric and young adult patients (age 19–39 years) within the INTERMACS database. Despite the expected differences in demographics, patient size and diagnosis, a composite outcome of survival to transplantation, ongoing support or recovery was similar between the groups (96 % for each) at 6-month follow-up. Adverse events and clinical outcomes were generally similar between the groups, although bleeding requiring surgical intervention was more common in the pediatric patients (11 vs 7 %) and length of stay was longer for pediatric patients compared to young adults (1.13 ± 0.85 vs 0.70 ± 0.45 months). While further study is needed to properly assess the risks inherent to implantation of continuous flow VADs in children, it appears that in the future continuous flow VADs may supplant pulsatile devices in larger children and adolescents.

As more pediatric patients receive long-term continuous flow devices, it will be important to assess the outcomes of the smallest patients as the devices were engineered to support adults with a much larger BSA (see Table 2) and the impact of a supra-normal cardiac output or attempts to

Table 2 Long-term ventricular assist devices—institutional recommendations

Device (manufacturer)	Position	Pump type	Minimum Patient Size	Flow range (L/min)
EXCOR® (Berlin Heart)	Extracorporeal	Pulsatile	No limit	Variable*
SynCardia® 70 cc TAH (CardioWest)	Corporeal	Pulsatile	>1.7 m^2†	<9.5
SynCardia® 50 cc TAH (CardioWest)	Corporeal	Pulsatile	>1.2 m^2†	<6.5
HVAD® (HeartWare)	Pericardial	Continuous	>1.5 m^2	<10
HeartMate II® (Thoratec)	Pre-peritoneal pocket	Continuous	>1.5 m^2	<10

* Dependent on pump size (available sizes 10, 15, 25, 30, 50, 60 ml)

† Best fit determined by fit study with 3D reconstruction and virtual surgery

modify pump speed below standards have not yet been established. Although not published, there have been greater than 100 implants of the durable continuous flow devices in pediatric patients with the smallest report of patients having a BSA of 0.7 m^2. Published reports will attempt to define adverse event rates and safety.

Pediatric Specific Issues

Biventricular Support

A critical decision when considering mechanical support is the use of a systemic VAD only or biventricular VAD (BiVAD). For a systemic VAD to function properly, you must have adequate right heart function to fill the systemic VAD. Adult studies report 19-44 % of patients experience some level of right ventricular failure following LVAD implantation [29, 48–50]. The rate of RVAD implantation in adults with the current generation of continuous flow devices is quite low (3–4 %) [29, 48]. Right ventricular dysfunction is associated with higher post-implant mortality in registry data [40] and smaller, focused studies [49, 51]. This has led to the development of risk scores in order to better stratify the risk of post-implant RV failure [49, 51] given the ~50 % mortality of patients requiring emergent RVAD implantation following LVAD placement [52].

Pediatric studies investigating right ventricular support are more limited. Early experience has shown implantation with an RVAD is more common in children. Thirty-six to thirty-eight percent of patients in the EXCOR IDE study required biventricular support [8•, 9•]. Other groups have reported similar rates of RVAD support, ranging from 25 [53] to 33 % [10]. Data suggests that the increased need for BiVAD support in pediatrics may be secondary to center experience and not necessarily due to a increased frequency of right ventricular failure. Data do show that children are considered for VAD support later in their course, usually following significant hemodynamic compromise, this may lead to an increased need for right heart support. The largest single-center experience in pediatrics describes a significant decrease in RVAD usage with program maturation without an adverse impact on outcomes [10]. Recent analysis of the EXCOR trial data also suggests decreased RVAD usage may be a significant opportunity to improve long-term morbidity and mortality [54]. This is further underscored by evidence suggesting that right heart failure rates were similar between pediatric patients and young adults in the largest study to date assessing pediatric continuous flow device use [47]. Short-term continuous flow RVADs may serve as a means to assess the need for long-term right ventricular support and thus decrease the need for long-term RVADs and the associated long-term consequences. This is especially relevant given that the development of the HVAD has allowed implantation of continuous flow VADs in patients with BSA <1 m^2 despite limited ability to decrease the VAD output accordingly. In theory, this supra-normal cardiac output supplied by an adult-sized device may result in extra stress to the child's right heart, although this has not been reported as an issue to date.

VAD Use in Congenital Heart Disease

Children with congenital heart disease (CHD) that require VAD support are at a higher risk of mortality when compared to children with cardiomyopathy [8•]. In multiple studies, CHD appears to be a risk factor, with the single ventricle population at the greatest risk [55•]. An ideal support strategy has not yet been defined for the single ventricle population, however, substantial effort has been made to establish a multi-institutional dataset to improve the outcomes of failing single ventricles [56]. Mechanical support has been reported after all stages of single ventricle palliation (systemic to pulmonary shunt, superior cavopulmonary anastomosis or Fontan completion). Mortality was very high (42 %) among functional single ventricles in the EXCOR trial, although the risk was not uniform across all stages of palliation [55•]. One of the nine patients who received an implant following their stage I palliation survived, while 58–60 % of patients supported following stage II or III palliation survived. While supporting the stage I patient is clearly challenging, alternate approaches to support including use of short-term,

centrifugal devices with EXCOR cannulas may improve outcomes by allowing teams greater flexibility in titrating device output to accommodate the fluctuating cardiac output needs of these patients.

There is suddenly an abundance of single ventricle patients that are reaching young adulthood that have had a Fontan completion and are presenting with heart failure. The "Failing Fontan" may be due to a single issue but is most commonly a result of a combination of the following; residual anatomic lesions, a restrictive systemic ventricle from chronic under filling, poor pulmonary architecture, chronic subclinical pulmonary emboli, and myocardial failure. The ideal support strategy depends on the etiology of the failure, but successful bridge techniques have ranged from using a continuous flow device to support the single ventricle to removing the ventricular mass and constructing a capacitance chamber to place a TAH-t [38, 47•, 57, 58]. Currently, the published experience suggests most centers will place a durable centrifugal pump as a bridge to transplant if the etiology of cardiac failure is isolated myocardial systolic dysfunction; however, this is rarely the case. Multiple studies have shown that while some patients have systolic dysfunction, the dominant phenotype in many long-term survivors is preserved, or relatively preserved systolic function, with evidence of gross diastolic dysfunction [59, 60]. In circumstances where a patient has significant diastolic dysfunction or residual structural lesions that need to be addressed, the TAH-t may be the most viable option for support [36•].

Optimizing "Device Fit"

The evolution toward implantation of intracorporeal VADs in children also poses questions of "fit" not relevant to most adult patients. While manufacturers provide general guidance regarding patient size, the trend in both adult and pediatric centers is to implant devices in smaller [41, 46, 47•]. This trend is not without risk as there are reports of complications due to patient-device mismatch [61]. In response, some centers have begun utilizing three-dimensional (3D), virtual device implantation to better define the limits of patient eligibility [35, 39•]. At our institution, all patients who are being considered for durable device placement receive a chest CT scan with 3D reconstruction to assess the feasibility of device implantation. This 3D model will allow for "virtual" surgery to occur prior to implantation. We believe this approach will allow centers to push the limits of size and also offer potentially creative approaches to device positioning. This is especially vital in cases with complex congenital heart disease that may require a novel surgical technique to optimize fit and flow. 3D printing technology may also play a role in assessing device fit. This technology has been used to help guide surgical planning in patients with congenital heart disease [62, 63] and we anticipate this will play a more significant role as we continue to implant adult-sized devices in pediatric patients. Over time we expect the availability of high quality, readily available 3D imaging will make general size recommendations more and more obsolete and device implantation will be dictated by team planning using modeling that incorporates patient-specific cardiac and thoracic anatomy.

Discharge of the Pediatric VAD Patient

With the use of adult continuous flow devices in children, pediatric VAD programs are now able to discharge select patients back into their community. Unlike large adult programs, that routinely discharge VAD-supported patients, most pediatric programs have limited discharge experience given the majority of their patients were in-hospital Berlin EXCOR patients. In the new era, the discharge process will be challenging, as even the largest programs will send only a handful of patients home per year. In addition, the discharge process will be complicated by additional unique training requirements, including schools, pediatric emergency rooms, and pediatric rehabilitation centers. Furthermore, future studies may reveal that pediatric patients may have age-related, outpatient, adverse events that have yet to be defined by the larger adult experience.

Unlike adult VAD discharge planning, the number of providers that needs to be trained is increased. Training materials must be adjusted by the implanting center to be age specific since all industry materials have been formatted for adults. Human factor testing should be considered for all devices that are not pediatric specific. Furthermore, education for the child and parents may be most effective by simulation training where troubleshooting scenarios are designed by the team and are then enacted with the family present.

Conclusions

In summary, the number of children with cardiac failure is growing; this has necessitated a rapid advancement in the field of pediatric mechanical support. In the last 5 years, the field has changed dramatically, from ECMO being the gold standard for almost all indications to individualized support that is tailored to the child's support need, anatomy, size, and heart failure etiology. The landmark event that has changed the field was the FDA approval of the Berlin Heart EXCOR. With this approval, pediatric centers have gained invaluable experience with VAD support that is changing the field of critical care, pediatric cardiology as

we speak. Centers have started implanting devices earlier to prevent end-organ dysfunction and are reconsidering the indications for biventricular support. With the field of pediatric mechanical circulatory support maturing, we have gained comfort and experience that is allowing us to extend the use of VADs to children of all sizes and anatomic configurations. Furthermore, a shift is occurring in the field where historically VADs were viewed solely as a bridge to heart transplant and now VADs being viewed more globally as a "bridge to decision". This allows the medical and surgical team to address the medical needs of the patient in a more stable and effective manner, while considering how to proceed the given long-term medical, social, and developmental needs of children and their families. Patient size, anatomy, and etiology of heart failure differ dramatically between children and adults; however, the differences in the social and developmental needs between children and adults with heart failure may be even more stark. Ultimately, one of the greatest impacts of the development of smaller, safer, and more effective durable devices may be that we can finally consider all of the ways children are not small adults.

Compliance with Ethics Guidelines

Disclosure David Morales has been a consultant; trainer, proctor and served on different committees and boards for Berlin Heart, Cormatrix and SynCardia. Angela Lorts and Chet Villa declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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