Review Article

Mechanical circulatory support in children: past, present and future

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Abstract: Rapid advances in the field of mechanical circulatory support (MCS) have dramatically changed the management of pediatric patients with heart failure. There is now emphasis on timely implantation of ventricular assist devices (VADs) to preserve or recover end-organ function, and increased focus on post-implant management to improve the stroke rate. Transplant waitlist mortality has significantly decreased in the era of VAD use. Devices approved for adults are being used off-label in children with excellent outcomes, allowing chronic therapy and discharge home to become part of pediatric VAD therapy.

Keywords: Mechanical circulatory support (MCS); pediatric; ventricular assist device (VAD)

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Introduction

Over the past two decades, the use of mechanical circulatory support (MCS) in children has greatly increased, specifically with respect to ventricular assist devices (VADs). Significant advances have been made in pump design, understanding of timing of implant, and improved post-implant management with respect to anticoagulation and blood pressure (BP) control. According to the Pediatric Heart Transplant Study (PHTS) initial report on VAD use, only 4% of patients listed for heart transplant from 1993 to 2003 were supported with a VAD (1). Currently, the use of VADs to bridge patients to transplant is becoming routine in pediatric centers with >40% of heart transplant recipients being bridged to transplant with a VAD, while recovery and even chronic therapy is being seen. The waitlist mortality for pediatric patients on the heart transplant waitlist has declined to around 8% in recent years, in large part due to increased VAD use (2).

History of MCS

Prior to the 2000s, patients requiring MCS as a bridge to transplantation typically received ECMO or an adult VAD placed in an older adult sized adolescent. In 2006, on behalf of the Pediatric Heart Transplant Study Investigators, Blume *et al.* evaluated children bridged to transplantation with a VAD. This study showed that survival to transplantation of children on VAD support (excluding patients on ECMO at the time of listing) was similar to those not requiring VAD. This first PHTS report demonstrated successful use of VADs as a bridge to transplantation in 86% of patients on device, though worse outcomes were seen among patients with congenital heart disease, and smaller size (1). This survival percentage was significantly higher than that reported for patients bridged to transplantation on ECMO (3-5). Various devices were used at that time, however the Berlin Heart EXCOR (Berlin Heart, AG, Berlin, Germany) gained momentum

in North America starting in 2004. In 2008, the EXCOR was approved for an investigational device exemption (IDE) trial, and after demonstrating significantly improved survival compared to patients on ECMO (6), the EXCOR gained FDA approval for use in pediatric patients in 2011. Though the EXCOR was the first widely used pediatric VAD, the MicroMed DeBakey VAD Child was the first VAD labeled for pediatric patients.

As technology evolved, and there was growth of smaller intracorporeal VADs in the field of adult MCS, pediatric centers began using VADs designed for adults in their larger pediatric patients. Additionally, as data emerged comparing pulsatile *vs.* continuous-flow devices, centers migrated towards continuous-flow pumps.

The use of MCS in pediatric patients has dramatically decreased waitlist mortality. When comparing 1999–2004 to 2005–2012, the waitlist mortality decreased by over 50% in the recent era (2). According to the 2019 Third Annual Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) report, from 2012–2017, greater than 500 devices were implanted at 30 centers, with over 750 devices in pediatric patients reported in total (7). With continued rapid growth in technology, VAD use in pediatric patients continues to expand to include support for patients with congenital heart disease as well as single ventricle physiology.

Present uses for MCS

The decision of when to utilize MCS is challenging, requiring careful consideration of underlying pathology, potential reversibility of myocardial dysfunction, timing of implantation, and anticipated duration of therapy. Additional factors such as patient size, and anatomy in the case of congenital heart disease, also play a role.

Timing of therapy

When patients in heart failure begin to develop end organ dysfunction (e.g., renal or liver failure), poor perfusion despite inotropic support, inability to tolerate enteral feeds, or need for intubation secondary to heart failure symptoms, a VAD should be considered.

It is known that both waitlist mortality and post-transplant survival are decreased in patients who have end organ dysfunction. Multiple studies have demonstrated that placement of a VAD improves renal function (8-11). Data from Pedimacs evaluating changes in renal function after VAD placement in 247 patients reported that pre-implant, 61% of patients had estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2, with a mean eGFR of 62.4±17 mL/min/1.73 m^2 (8). At 1-month post-implant among those who had baseline renal dysfunction, 67% of patients alive on VAD support had normalization of eGFR (mean eGFR 107.7±39.6 mL/min/1.73 m^2). Another study using Pedimacs-PHTS data describes that patients requiring VAD implant have end organ dysfunction, require mechanical ventilation and more inotropic support than patients waitlisted without MCS, but after VAD placement, there is normalization of renal function (12) and these patients are known to have the same survival as those transplant patients who were not bridged with a VAD. Since renal dysfunction is associated with poor post-transplant outcomes (13,14) and increased risk for in-hospital mortality (15), efforts should be made to implant a VAD prior to development of irreversible renal injury. Philip *et al.* report persistent renal dysfunction 2 weeks post VAD was associated with increased mortality (10).

Post VAD implant, patients are also able to wean off inotropic agents as the device provides the necessary cardiac output. Vasoactive agents to control systemic vascular resistance (SVR) may continue to be used in cases of either hypertension, or with vasodilation during an inflamed or infected state. Extubation is a primary goal following VAD implant, as waitlist mortality is higher and post-transplant survival is lower in intubated patients (1,2,13).

Temporary support

Extracorporeal membrane oxygenation (ECMO) continues to be utilized frequently across North America and internationally. Extracorporeal membrane oxygenator support is an ideal strategy in cases where pulmonary, combined cardio-pulmonary support, or immediate support (i.e., ECPR) is needed; however, we should attempt to avoid it in patients with isolated heart failure as hospital mortality exceeds 40%, even in the recent era (16,17). Among patients requiring ECMO support, 52% were for cardiac support (17) with survival rates of 40% for neonates <28 days of age, and 49% for pediatric patients between 28 days of life and 17 years (17). Unfortunately, survival for congenital heart disease across age groups is inferior to that for patients with myocarditis (67% survival) and cardiomyopathy (56% survival) (17).

Temporary support is typically used to support patients with cardiogenic shock as a bridge to recovery, bridge to durable VAD, or bridge to decision. It can be used for

patients with myocarditis, those developing shock during cancer therapy, or transplanted patients with acute rejection. The VAD in these cases is supporting the circulation, while the inflammation causing myocardial inflammation resolves, allowing in many cases for the VAD to be removed. The primary advantage and distinguishing factor are that cannulation can typically be performed off cardiopulmonary bypass, with paracorporeal centrifugal pumps. However, a more recent approach across centers for bridging smaller patients or those with single ventricle heart physiology to transplant has been to cannulate on cardiopulmonary bypass with Berlin Heart cannulas, and centrifugal pumps such as a CentriMag (Abbott, IL, USA) or PediMag (Abbott, IL, USA). This technique allows higher flows (18), and a more stable cannulation strategy with ability to easily exchange pumps during long-term support (19). In the event of worsening respiratory status, this setup also allows for an oxygenator to be spliced into the circuit.

For larger patients, the Impella devices (Abiomed, MA) and TandemHeart (CardiaAssist, PA, USA) can offer percutaneous support. The Impella 2.5, CP, and 5.0 devices are axial flow devices that sit across the aortic valve to provide continuous forward flow from the left ventricle to the aortic root which both augments cardiac output, and decompresses the heart. When used in pediatric patients, a graft has often been sewn to the innominate artery as non-traumatic way to implant the Impella. The Impella RP provides right heart support, propelling blood from the right ventricle to pulmonary artery. Successful biventricular Impella support as a bridge to recovery or transplant has been reported in adult literature (20-22), and first use of biventricular Impella support in a pediatric center was described in 2018 (23). The venous inflow for the TandemHeart requires puncturing of the atrial septum from right-to-left and its precise placement and inflow can easily be affected with small movements of the patient making it less desirable in pediatrics.

Long-term or chronic support

Long-term support is typically achieved through two groups of devices—intracorporeal continuous-flow and paracorporeal pulsatile devices. Previously, infants and small children with and without congenital heart disease were bridged to transplant with the Berlin Heart EXCOR, the only presently FDA approved device for pediatric patients. Now, for small single ventricle patients, many centers use Berlin Heart cannulas with a continuous flow pump (i.e., CentriMag) to achieve the necessary flows for optimal support. For infants and children with biventricular circulation, weighing up to 20 kg, the Berlin Heart EXCOR is typically still used.

According to Pedimacs, the pediatric section of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), among pediatric patients, the most commonly implanted intracorporeal continuous flow device is currently the HeartWare HVAD (Medtronic, MN). Though this device is not approved for use in pediatric patients, it has been used as long-term therapy for patients with a BSA of down to 0.6 m^2 (24). A multi-center, international study evaluating the use of HVAD in pediatric patients reported comparable survival to adults, with a 90% positive outcome at 12 months: 46% of patients transplanted or explanted, 44% remaining on device therapy, and 10% who died post implant (25).

Between 2012 and 2017, Pedimacs reported 197 children <19 years of age who underwent HVAD implant (26). The weight ranged 13.1 to 162 kg, with 12 patients <20 kg of which 58% had congenital heart disease. The median BSA was 1.5 m^2 (range, 0.6–2.9 m^2). Adverse effects including bleeding (23%) and stroke (10%) were no different in the pediatric cohort when compared to young adults age 19–30 years (23% and 12% respectively), with lower reported infections (27% *vs.* 44%) and device malfunction or pump thrombosis (11% *vs.* 19%) in the younger group. This suggests this device can be successfully used in pediatric patients requiring advanced heart failure therapies.

The HeartMate 3 (Abbott, Chicago, IL, USA), a magnetically completely levitated device designed for reduced thrombotic and hemolytic complications, was FDA approved for use in adults in 2017 and since then has largely replaced the use of other intracorporeal devices in the adult US field. In the adult Momentum 3 trial which compared it to the HeartMate 2 (Abbott, Chicago, IL, USA), the HeartMate 3 was found to have a lower rate of stroke (10.1% *vs.* 19.2%), and fewer reoperations for pump malfunction (1.6% *vs.* 17%) than its predecessor (27). There was no difference in mortality.

Pediatric centers began implanting the HeartMate 3 in 2017. By 10/21/18, according to O'Connor and colleagues who report on data from the Advanced Cardiac Therapies Improving Outcomes Network (Action), 14 HeartMate 3 devices were implanted at 6 centers (28). In their report, the majority of patients (13/14, 93%) had a diagnosis of dilated cardiomyopathy, with a single patient (7%) having congenital heart disease (Fontan). Of those with dilated cardiomyopathy, 3 patients had neuromuscular disorders.

Median weight was 70 kg (range, 31–118 kg) and median BSA 1.8 m^2 (range, 1.3–2.4 m^2). The duration of support for patients with the HeartMate 3 device ranged 5 to 315 days, and at the end of the study period, 93% had a positive outcome and 36% were discharged. There was 1 death (7%) with no reported pump thrombosis or stroke (28). Since this initial study reporting on the use of HeartMate 3 in pediatric centers, there have been multiple additional implants in patients with dilated cardiomyopathy, as well as congenital heart disease with current numbers estimated at approximately at 40. At the authors' own institution, as of May 2019, 9 HeartMate 3 devices have been implanted, with the lowest patient weight of 27 kg who was successfully transplanted, and 45% of these patients implanted as chronic VAD therapy (2 patients with Duchene's Muscular Dystrophy; 1 Fontan, 1 Atrial switch). With such excellent outcomes, it is becoming the preferred device in pediatric patients >25 to 30 kg.

The only pulsatile device used for older children and adult patients is the SynCardia Total Artificial Heart (TAH) (Tucson, AZ, USA). There is both a 70-cc pump available (predominately for patients with a BSA >1.7 m^2), and a 50-cc pump (for patients with a BSA between 1.2 and 1.85 m^2) under trial. Over the past decade, technology has emerged allowing "fit testing" or virtual implantation of a select device into the thoracic cavity of a specific patient which allows case-by-case or individual implantation planning regardless of BSA (29). This work has led to the FDA allowing virtual implantation to be an acceptable criterion for sizing in an FDA trial (50/50-cc SynCardia Pediatric Trial). The TAH is currently used as a bridge to transplantation, but destination therapy is being studied. In pediatric patients, the TAH has been used for cases of ventricular clot burden, congenital heart disease unamenable to left VAD (LVAD) support (i.e., right ventricular to pulmonary arterial (RV-PA) conduit, or valve regurgitation), and primary cardiac arrhythmias (30). Other uses for the TAH have included transplanted patients who require MCS, as placement of the TAH allows immunosuppression to be stopped and thus reduces the risk of bacterial or fungal infections. Additionally, the TAH implant has been used in patients with failing Fontan circulation as it not only promotes cardiac output, but can also lower the CVP (31).

Biventricular support

Biventricular VAD (BiVAD) support continues to be utilized in select clinical scenarios, but frequency of use has declined over the past decade with improvements in decision making. According to the 3rd Annual Pedimacs report, 15% of patients were supported with BiVAD strategy (7). The decline in use may be due to multiple studies reporting worse outcomes for pediatric patients supported with BiVAD pumps, and concentrated efforts to use them judiciously. The Berlin Heart EXCOR Pediatric IDE study reported biVAD support was a predictor of early mortality (32). According to Zafar *et al.*, patients who were implanted with biventricular Berlin Heart EXCOR devices did not show improved survival and actually had increased mortality if bridged on ECMO to BiVAD (33). Patients who were placed on ECMO prior to BiVAD placement had increased mortality, as well as BiVAD patients with abnormal GFR, smaller pumps (10 mL), white race, and sites who implanted <5 devices (33).

A study of adult patients using INTERMACS by Arabia et al., demonstrated that most adult patients implanted with the TAH for biventricular dysfunction were INTERMACS profile 1 (34), with better outcomes than previously reported with BiVAD HVAD support. Although BiVAD intracorporeal devices are often discussed, a small number are implanted in North America per year. Despite this, there are most certainly patients who need and would benefit from BiVAD support (approximately 5–15% in the pediatric field), but this needs to be further studied to identify the correct population and predicting which right ventricles will fail with LVAD support. The authors believe that the need for BiVAD support is probably mostly HF etiology driven and timing of implantation.

Supporting single ventricle physiology

MCS for patients with CHD is challenging, specifically in patients with single ventricle physiology. Given that the highest mortality for patients on the heart transplant waitlist is among infants less than 1 year of age (35) and those with congenital heart disease, creative strategies have been employed to support this group. Attention must be paid to cannulation techniques given variable anatomy, and type of pump needed to achieve target flows.

Cannulation for single ventricle patients is typically via the common atrium and aorta/neo-aorta. Pulmonary blood flow is delivered through either a Blalock-Taussig shunt, native pulmonary arteries, the bidirectional Glenn (BDG), or Fontan circuits. If a patient has an RV to PA conduit providing pulmonary blood flow, this will have to be converted to a systemic to PA shunt if a VAD is to be

placed. Patients with shunted circulation are particularly challenging as there is no good way to alter or predict the flow going through the shunt, and patients may develop over-circulation at the high flows required to perfuse the body. Likewise, in failing BDG or Fontan circulations, the multiple aorto-pulmonary collaterals make it difficult to predict output requirements and manage the everchanging inflow volume, making support with fixed volume devices (i.e., EXCOR) difficult. This issue can lead to pulmonary edema, or even need for intubation requiring significant diuresis balanced against the development of acute kidney injury.

In supporting a single ventricle patient after either the Norwood operation or BDG, a device must be chosen that can provide high flows, up to a cardiac index of >5 L/min/m^2 in most cases. For the 1st stage palliation, high flows are required to support both the systemic and pulmonary circulations. Post BDG, patients typically have a high flow requirement secondary to aorto-pulmonary collaterals. A now common technique for both short- and long-term support has been the placement of Berlin Cannulas with an extracorporeal continuous flow pump. This strategy allows for long-term support with a device that can easily adjust to fluctuating vascular resistance and collateral circulation. Patients have been well supported with this strategy, tolerating feeds, able to be extubated, and may achieve some rehabilitation. Some centers will exchange the continuous flow device to a Berlin Heart EXCOR when the patient reaches the point of rehabilitation—this pump, however, may limit the amount you are able to increase your flows.

The outcomes are overall poor for patients supported with VAD after stage 1 palliation, such as described by Weinstein *et al.*, who reported only 1 of 9 patients in the series surviving, the rest dying within 3 weeks of device implantation (36). The surviving patient was not a typical Norwood and was significantly older at VAD implantation. To date, no reports exist of a neonatal single ventricle patient post Norwood procedure being bridged to transplant with an EXCOR VAD and surviving to discharge home. However, there are multiple successes occurring now with the use of extracorporeal continuous flow devices. Patients with a BDG supported with the Berlin Heart EXCOR to transplantation have had better outcomes, with 7 of 12 surviving to transplantation (36). However, as stated, the current strategy for BDG patients in most centers is the use of extracorporeal CF VADs.

In Fontan patients, it is important to note that the Fontan fails at multiple levels and is rarely isolated failure of the systemic ventricle. One must take an inventory of the causes of failure for that patient's particular Fontan circulation failure and decide if the failure is dominated by right sided or left sided lesions. This cannot truly be assessed without catheter data and knowing the end-diastolic pressure. If it is low (i.e., <12 mmHg) it is doubtful that a systemic VAD (SVAD) will benefit that patient a lot. A VAD will provide minimal support to right-sided failure. Though there is ongoing research in sub-pulmonary assistance for Fontan patients (37,38), the focus has changed to supporting Fontan circulations before failure to avoid the chronic complications occurring from passive pulmonary blood flow. Once the Fontan circulation has failed, a sub-pulmonary VAD forcing blood through an abnormal pulmonary circulation into a restrictive systemic ventricle is not a long-term solution (39). When systolic or diastolic dysfunction is the etiology of the patient's symptoms, a VAD can be highly effective in supporting Fontan patients to transplantation. In select cases when the patient has end-stage symptoms (i.e., hepatic congestive "cirrhosis", renal insufficiency, PLE; plastic bronchitis), a TAH should be considered since this patient is a poor VAD or transplant candidate. The TAH will not only provide supra-physiological cardiac output, but more importantly it has the ability to significantly decrease the central venous pressure to near zero and is unachievable even with a cardiac transplantation. This will be key in resuscitating these patients to become good transplant candidates.

Adult congenital heart disease (ACHD)

The number of adult patients with congenital heart disease is growing, with over 1 million people estimated to be living with CHD in the United States (40-42). Patients with both single ventricle physiology who are post Fontan, as well as patients with biventricular repairs are developing heart failure decades after their surgical repairs. MCS has been used with increasing frequency in this population, utilizing different techniques for different lesions (43), and outcomes in patients with two ventricle physiology supported with an LVAD have been similar to patients without congenital heart disease (44). A review of the INTERMACS registry looking at VAD support for ACHD patients compared to patients without congenital heart disease revealed similar survival in the 2 groups among patients who underwent LVAD only implant (45). Patients with ACHD had higher proportion of BiVAD or TAH use compared to non-ACHD patients, and the mortality rate was higher for this group

on BiVAD support or TAH implant (45,46). Surprisingly, morbidity, functional status and quality of life post MCS among patients with ACHD was similar to patients without ACHD (46). Overall, it is known that VADs are underutilized in the ACHD population even though reported outcomes are similar to non-ACHD patients, and more aggressive use of VAD therapy in this population may be advisable.

Future directions

New devices and expanded use of current pumps

With improved imaging technology and ability to perform fit studies, devices such as the HeartMate 3 are able to be implanted into smaller patients.

The conventional method of implantation for the HeartMate 3 and HVAD devices is via median sternotomy with outflow graft anastomosis to the ascending aorta. Multiple reports from adult centers describe alternative implant techniques such as lateral thoracotomy with outflow graft connect to descending aorta (47-49). This technique may be useful in patients with multiple prior sternotomies in whom an additional sternotomy may be avoided prior to transplantation.

For small children (8–20 kg), the Jarvik 2015 (Jarvik Heart, NY, USA) is currently being studied through the Pumps for Kids, Infants, and Neonates (PumpKin) trial. This small (size of an AA battery), intracorporeal, continuous flow axial device was developed by the pediatric Circulatory Support Program within the National Heart, Lung and Blood Institute. Its first reported successful use was in 2018 in a 4-year-old female (BSA 0.5 m^2, weight 12 kg) who at 3 weeks post implant had normal end organ function, was tolerating oral feeds and was ambulatory (50). The device is in a feasibility study which allows continued development of the device as clinical cases are performed and presently the device protocol and management are being re-assessed.

Collaboration and quality improvement

In 2017, the Advanced Cardiac Therapies Improving Outcomes Network (Action) was established. This learning network aims to improve care for patients with VAD support at pediatric centers, and has enjoyed significant growth with >30 participating centers, estimating that it captures >80% of all VADs placed in pediatric centers in the USA (51). There is now an increasing membership of international centers. There are quality improvement arms, registry data collection, as well as educational materials (both online interactive platforms and infographics) available to all participants to standardize care for patients with VAD support. The collective wealth of outcomes is paramount to advancing the field for this group of patients as most centers have <10 implants annually. Furthermore, if multiple centers can follow similar protocols, we can adjust management across a larger number of patients to allow for more powerful analyses and clearer results. Along with parents and patients who are vital members of ACTION, stroke was chosen to be the first QI initiative. Over an 18-month focused commitment to a three-prong approach (i.e., anticoagulation harmonization using Bivalirudin, BP control and communication in the ICU) stroke in the Network participating centers has decreased 50%. Through quality improvement work in Action, guidelines and protocols are being created to ensure optimal care for all patients post VAD implant, with continued emphasis on improvement and collaboration among centers.

Anticoagulation

Typical anticoagulation strategies for older children and adolescent patients on continuous flow durable devices (HeartMate 3 or HeartWare) include heparin infusions until they are bridged to therapeutic warfarin. There has been a move away from heparin to bivalirudin for smaller patients supported with either the Berlin Heart EXCOR, or continuous flow centrifugal support (CentriMag or PediMag) with either temporary or Berlin cannulas.

Aspirin is typically used for antiplatelet therapy, with some centers also using dual or triple antiplatelet therapy (adding dipyridamole or clopidogrel). Individual centers have reported a decreased stroke rate with triple antiplatelet therapy, though other factors may have contributed such as higher doses as well as steroids in times of inflammation (52).

BP control

BP management is critical as continuous flow centrifugal pumps are sensitive to afterload. Fluctuations in BP, as well as hypertension can lead to increased stroke risk (ENDURANCE trial) with multiple adult studies demonstrating improved stroke rate in patients with good BP control (53-55). The ENDURANCE Supplemental Trial showed that after implementation of a BP management

protocol in patients with an HVAD, there was a 50% hemorrhagic stroke reduction and 24.7% combined reduction of ischemic and hemorrhagic strokes (56). Through the Action Learning Network, BP guidelines for pediatric centers have been created.

Conclusions

VADs are being used with increasing frequency in pediatric patients and ACHD patients with heart failure. With increased attention to device selection, timing of implant, individualized fit, and post-implant management, we continue to improve our outcomes to bridge to transplantation, to recovery and as destination therapy. Our fields' commitment to cooperation and not competition via the learning network ACTION is allowing us to make great progress as a field in general for all our patients and families, and at a much more rapid pace than traditional academic medicine.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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