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Ventricular assist device use in congenital heart disease with a comparison to heart transplant

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Abstract

Despite advances in medical and surgical therapies, some children with congenital heart disease (CHD) are not able to be adequately treated or palliated, leading them to develop progressive heart failure. As these patients progress to end-stage heart failure they pose a unique set of challenges. Heart transplant remains the standard of care; the donor pool, however, remains limited. Following the experience from the adult realm, the pediatric ventricular assist device (VAD) has emerged as a valid treatment option as a bridge to transplant. Due to the infrequent necessity and the uniqueness of each case, the pediatric VAD in the CHD population remains a topic with limited information. Given the experience in the adult realm, we were tasked with reviewing pediatric VADs and their use in patients with CHD and comparing this therapy to heart transplantation when possible.

Keywords

congenital heart disease; heart failure; heart transplant; pediatric; single ventricle; ventricular assist device

Background

Heart failure represents a significant problem in the pediatric population causing over 10,000 hospitalizations per year [1]. The causes consist mainly of acute myocarditis, dilated cardiomyopathy (DCM), chemotherapy-induced cardiomyopathy and congenital heart disease (CHD). Heart transplant (HT) has been, and remains, the standard of care for end-stage heart failure. Unfortunately the donor pool remains limited allowing only 350–400 transplants per year (Figure 1). As a consequence, mortality while on the 'waiting list' is not an infrequent occurrence for these children. Traditionally, mechanical circulatory support (MCS) in the form of extracorporeal membrane oxygenation (ECMO) has been utilized to bridge the sickest patients to transplant. ECMO support for these children, however, has

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significant limitations, allowing very few patients to be supported long enough to reach transplant with many suffering significant adverse events. For this reason, the ventricular assist device (VAD) has emerged as a superior option for many pediatric patients, much as in the adult world. As of the 2013 International Society for Heart and Lung Transplantation (ISHLT) report, a VAD or total artificial heart is now utilized as a bridge to transplant (BTT) in over 20% of pediatric HT recipients [2].

However, VADs are not being equally applied to all pediatric patients awaiting transplantation. Heart failure in patients with CHD represents a significantly different problem than in those with heart failure secondary to an infectious or drug-induced cause. Many of the CHD patients have undergone multiple prior palliative surgeries and are therefore, presenting for VAD placement as their fourth or fifth procedure. Further, many of these patients have complex anatomic and physiologic substrates; many are single ventricle (SV) patients, wherein the systemic circulation is supported by one pumping chamber while pulmonary blood flow is maintained through passive, shunt-dependent flow. Many of these patients also suffer from significant comorbidities, accumulated over repeated hospital encounters or as a result of their underlying pathophysiology. Some CHD lesions cause considerable, occasionally irreversible, effects such as pulmonary hypertension. These patients not uncommonly have other congenital anomalies that can impact transplant eligibility or feasibility of VAD placement. For CHD patients that survive to adulthood, many have noted an increased risk of adverse cardiovascular events, including heart failure, even with less severe anatomical defects [3]. Despite these challenges, a VAD offers many advantages including allowing a longer duration of support, possibility of extubation, increased mobility, participation in rehabilitation and the possibility of hospital discharge [4]. Therefore, it is imperative to better understand the challenges and key factors that could impact heart transplantation and MCS in both children and adults with CHD.

In this article we examine the recent literature evaluating outcomes for pediatric patients who underwent VAD placement in the context of candidacy for transplantation, and briefly discuss destination therapy (DT). The focus will be on patients with heart failure due to CHD. Comparison will be made to pediatric HT where applicable.

Heart transplant

HT is currently the best long-term treatment option for pediatric patients with end-stage heart failure. Survival rates vary significantly when considering different age groups and indications for HT, with a higher rate of survival with younger transplant recipients. Currently, infants receiving an HT have an expected survival of almost 20 years [2]. CHD is the indication for greater than 50% of pediatric HTs, a substantial portion of which are for SV patients [5]. Unfortunately, patients with CHD have a lower survival rate after HT, with a significant portion of the mortality occurring within the perioperative period [6]. The ISHLT data note a hazard ratio of 2.04 in patients with a pretransplant diagnosis of CHD [2]. Despite the lower survival rate among patients with CHD, HT remains their best long-term option. The 5-year survival after HT of a large group of CHD patients, all greater than 6 months of age, was 80% in one multi-institutional study [6].

Ventricular assist device

Since the REMATCH trial showed superiority of the VAD in adult patients for DT, the VAD has become a well established treatment option for the management of end-stage heart failure in adults for both BTT and DT [7]. The pediatric population, however, has posed some unique challenges. Specifically, pediatric patient's small size requires a smaller device that can be supported by their frame, as well as provide low enough flows without thrombus formation. This is further complicated by the less understood pediatric coagulation system when compared with the adult. Further the necessity of pediatric VADs is far less than that of adults, thus reducing the financial incentive for device companies to pursue development of pediatric specific VADs. For these reasons, the development of VADs in the pediatric population has lagged that of adults and they did not come into widespread use in the USA until 2004.

The Berlin Heart EXCOR (Berlin Heart Inc., Berlin, Germany) IDE study showed safety and efficacy of the pediatric VAD, and with this the use of pediatric VADs has increased significantly [8]. Subsequently, adult VADs have shown utility in the larger pediatric population. Since the IDE study, multiple reports have investigated the utility of VADs in the pediatric population with a survival rate between 75 and 100% and a longer duration of support than possible with ECMO (Table 1) [9–18]. Recent data have suggested that patients who receive VAD support prior to HT have equivalent survival to those who do not and an improved survival over patients supported with ECMO [2,19].

Available devices

Pulsatile flow: Berlin EXCOR

The Berlin Heart EXCOR is the original VAD approved for placement in pediatric patients with end-stage heart failure. It is a pneumatically driven pulsatile device that is available in different sizes to support a range of pediatric patients (Figure 2). Due to the pulsatile design, two biological valves are necessary. It can be utilized on its own or in combination for biventricular assist device (BiVAD) support. It allows for patient extubation, participation in rehabilitation exercises and utilization of enteral nutrition. It is not, however, approved to allow for patient discharge in the United States.

Continuous flow: HeartMate II & HeartWare HVAD

With decreased size and improvement in adult devices, many of these can be adapted to larger pediatric patients with excellent outcomes [15,16,20,21]. With a continuous-flow design, valves become unnecessary. This allows for fewer moving parts and increased device durability. The HeartMate II (Thoratec Corp., CA, USA) and HeartWare HVAD (Heartware Inc., MA, USA) have both been utilized off label in pediatric patients. The HeartMate II (Figure 3A) is a small axial flow device that sits in a surgically created pocket [22], and the HeartWare HVAD (Figure 3B) is a small intrapericardial centrifugal flow device [23]. Both can be used in larger pediatric patients, with the HeartWare being potentially utilized in patients with a BSA as low as 0.7 m² [24]. With the proven benefits of the continuous-flow devices, including increased mobility with a smaller device and the possibility of discharge, these devices are now frequently considered in any patient who is

large enough to receive one. The intrapericardial location of the HVAD has made that device particularly attractive to the pediatric practitioner.

Short-term devices: CentriMag/PediMag, TandemHeart & Impella

The CentriMag (Thoratec Inc., CA, USA) is an extracorporeal centrifugal pump. A smaller version, the PediMag (Thoratec Inc., CA, USA), has recently been introduced for the infant population [25]. These have been utilized in the pediatric population for short-term cardiac support, commonly as a bridge to decision (BTD) [26]. Some have used the cannulas of a longer term device, such as a Berlin Heart, with the more short-term devices, such as a CentriMag, to facilitate an easy transition from BTD to BTT [27].

The TandemHeart (CardiacAssist Inc., PA, USA) consists of a femoral venous cannula placed into the right atrium or transeptally into the left atrium connected to a centrifugal pump with the outflow into the arterial system. Though an adult VAD, it has been used in the pediatric population [28]. The Impella (Abiomed Inc., MA, USA) is an axial flow device placed percutaneously via the femoral artery, with fluoroscopic or echocardiographic guidance, across the aortic valve. It is available in different sizes and more commonly used in adults for partial cardiac support, but has also been described in the larger pediatric population for temporary support [29,30].

Indications for VAD

The indications for VAD placement are significantly different in the pediatric population than in the adult. Specifically, nearly all pediatric patients currently have a VAD placed as BTT, where as in the adult population DT makes up 44% of the indications, a number that is increasing rapidly [31]. The pediatric population may end up having a larger portion of patients who transition from BTT to bridge to recovery (BTR), or have the VAD placed anticipating recovery, but this is still a matter of speculation. Likely, for CHD patients, however, since the underlying anatomy and physiology is not adequate, the greater role for VADs will be for BTT or DT. BTD is a rare indication in the pediatric population, but may become more common place with increasing experience. In particular, due to challenges with limited number of donors and the greater scrutiny on outcomes, it is conceivable that more pediatric programs would use VADs as an option to 'improve' patient status and clarify eligibility prior to listing the patient for HT.

DT for the pediatric population could be an option for patients not deemed candidates for transplantation. Pediatric DT has been described in the treatment of DCM in patients with Duchenne's muscular dystrophy with a duration of support greater than 10.4 months at the time of their publication [32]. Dramatic increases in survival have been noted in the adult population with improved devices, improved postoperative care and better patient selection. If similar strides are made with pediatric VADs, strides that are not mirrored by that of HT, it is conceivable for the VAD to be utilized more commonly as DT in pediatric heart failure. In particular, pediatric patients with limited or high-risk surgical palliative options can be funneled down the DT pathway; in other words, complex reconstruction plus VAD therapy in lieu of surgery alone. With the development of appropriate devices, this could likely be the largest DT use of VADs in children.

VAD in CHD

Many studies have evaluated the use of pediatric VADs; however, few have looked specifically at the population of patients with structural cardiac abnormalities. When analyzing the CHD subsets in larger studies of pediatric patients with heart failure, the CHD patients seem to have an overall worse survival [19]. However, conclusions regarding CHD patients in these papers have to be drawn with some caution due to many confounding factors that cannot always be taken into account [33]. A study analyzing MCS use in 29 patients with CHD, 14 with SV physiology, showed 72% survival to HT and 59% survival to discharge [34].

Single ventricle patients

The population of patients who have undergone conversion to SV physiology and subsequently develop heart failure presents a unique challenge to the physician caring for these pediatric, and now adult, patients. The existing data evaluating the use of a VAD in pediatric patients with an SV consists almost entirely of case reports [35–40]. To address this heterogeneous, uncommon and increasing problem a registry has been devised for reporting these patients [41]. In one of the larger studies to date (26 pediatric patients) evaluating VAD use in SV patients, Weinstein *et al.* reported that VAD placement can be performed successfully, though with worse outcomes than in patients with biventricular physiology, with a survival rate of 42% following VAD placement [42]. Long-term support has been demonstrated [43], which is particularly important for CHD patients due to longer anticipated HT waiting times. Interestingly, one case report did employ VAD assistance for the systemic circulation for 6 months after a Fontan and the patient was able to be bridged successfully to recovery [38].

The altered Fontan anatomy makes implantation of the VAD difficult and the complex physiology further complicates matters. There are different surgical options with significantly different implications. Most commonly, a VAD is inserted into the apex of the ventricle and the outflow to the neo-aorta. Alternatively, utilizing a VAD to supply the pulmonary blood flow, BiVAD configuration, becomes quite challenging in these patients. It requires takedown of the Fontan pathway because placement of an inflow cannula in the total cavopulmonary connection and an outflow in the main pulmonary artery would otherwise cause a substantial amount of recirculation [44]. Others have tried to accomplish this goal by separating the ‘right side’ and creating a neo-right ventricle, with an associated VAD, to increase preload to the systemic ventricle. Overall, many believe that failing Fontan physiology represents a significant problem with a worse expected outcome with either transplantation or MCS [45,46].

Adults with surgically repaired CHD

As surgical and medical management of CHD has improved, more of these patients are living into adulthood. It is anticipated that a significant portion of these patients will eventually develop heart failure. The utility of a VAD, if MCS becomes necessary, is obvious as these patients have had multiple cardiac operations and transfusions, so not uncommonly they will have a long wait on the HT list. Unfortunately, limited data exist to

guide the physician in this situation. One study focusing on three adult patients with a history of transposition of the great arteries (TGA) and a systemic right ventricle found a VAD can be useful as a bridge to transplant [47]. They found use of intraoperative epicardial and transesophageal echocardiogram allowed for placement of the inflow cannula with avoidance of the moderator band improved inflow. A larger study of six patients with a systemic right ventricle, four biventricular physiology and two SV physiology, has shown good results for BTT and DT with 83 % surviving more than 150 days on support [48]. A recent case report of a patient with congenitally corrected-TGA (CC-TGA) and severe pulmonary hypertension showed VAD use allowed for reversal of the pulmonary hypertension and for an HT alone instead of a heart-lung transplant, which was previously considered necessary [49].

As the first surviving Fontan patients reach middle age, physicians will be faced with difficult questions as many of these patients' SV may begin to fail. They have unknown long-term outcomes and the use of a VAD in these patients is largely unstudied. One case report discussed the treatment of a young adult with SV physiology who developed heart failure and was treated with a right ventricular assist device (RVAD) after Fontan takedown; he survived 13 months to HT [50]. Another case highlights VAD use in the acute postoperative period after attempted Fontan revision in an adult with a failing Fontan. The VAD was placed to support the systemic circulation and allowed for patient discharge and HT 5 months after VAD implantation [51].

VAD complications

Though VADs have clearly shown an increase in survival, it is not without complications. Common complications include infections of the drive-line or the device hardware itself, hemorrhage, cerebrovascular events including hemorrhagic or thromboembolic, increase in panel reactive antibodies (PRA) and right heart failure. These can lead to increased need for medications, inotropic support, pump changes, RVAD implantation or death. Hemorrhage is typically defined as requiring multiple transfusions or reoperation and occurs in 22–50% of patients [8,52]. The risk of infectious complications is seen in 35–52% and is managed with broad spectrum antibiotics and antifungals [8,52]. Every effort must be made to clear the infection prior to the initiation of immunosuppression that will be required with a transplant.

Risk of cerebrovascular event

A cerebrovascular event (CVE) can be a devastating complication and occurs with an incidence of 29% [8]. Thromboembolic strokes are more frequent; however hemorrhagic strokes tend to be more devastating. The risk of CVE is clearly impacted by the anticoagulation regimen, with a higher incidence of CVE occurring in patients who have not yet reached their target anticoagulation goals. Due to improved management of anticoagulation regimens, the greater participation of hematologists in the care team and more aggressive management of pump thromboses with pump changes, the risk of CVEs is decreasing [53].

Increase in HLA sensitization

The use of a VAD in adults has been shown to increase a patient's PRA, more significantly with pulsatile than continuous-flow devices [54,55]. VADs have been shown to lead to an increase in PRA in as high as 35% of pediatric patients, though no change in survival was noted [56]. An increased risk of rejection was seen in patients who were supported with the EXCOR versus those not requiring MCS, which is consistent with the increased rate of primary graft dysfunction seen in adults with elevated PRAs after VAD use [19,54]. The reason for the elevated PRA is unknown, but hypotheses include formation of antibodies from exposure to artificial material and biological valves, increased inflammatory response with VAD support and the exposure to an increased number of blood products, though the impact of blood product transfusion has been discounted in some studies [55,56].

Gastrointestinal bleeds

Gastrointestinal bleeds is an intriguing and poorly understood complication that is associated with continuous-flow devices. It is thought to occur as a result of an acquired von Willebrand syndrome in combination with a decreased pulse pressure causing GI tract arteriovenous malformations [57]. This complication, seen in the adult population [58], is not as common in the pediatric literature, though one patient has been reported to develop an acquired von Willebrand syndrome [15]. It is however, something to consider as the number of continuous-flow devices used in the pediatric population increases in addition to the increase in duration of support.

Right ventricle failure

One of the more important decisions when placing a patient on MCS is the evaluation of right ventricular function. BiVAD was initially utilized by some institutions almost universally. However, it is commonly accepted that BiVAD support results in a decreased, but still reasonable, survival of 62–89% [33,59–61]. While the severity of illness is likely a confounding factor, a second VAD would expose the patient to an increased risk of complications. They still remain more commonly utilized in the pediatric population due to the pathology, as recent studies suggest that some degree of right ventricular dysfunction may be universal in pediatric DCM [62]. Currently BiVAD support is utilized in approximately 25% of pediatric patients [61]. One recommended algorithm for potential RVAD placement at the time of LVAD (left ventricular assist device) placement was proposed by Stiller *et al* [60]. They recommend the decision be made in the operating room after placement of the LVAD. The drainage provided by the LVAD may decrease the pressure in the left atrium, afterload of the right ventricle, enough to allow the right ventricle to function with the aid of inotropic support but without mechanical support.

Impact on transplant match

As data continue to accumulate illustrating the utility of a VAD for BTT, more VADs will be placed. This, in combination with the duration of support possible with a VAD, will result in more patients on the HT waiting list [13]. With these longer waitlist times and a larger waitlist pool, comes the potential for better transplant matches. Ideally this would lead to fewer hospitalizations for rejection and fewer biopsies necessary for diagnosis and

surveillance. This may be offset, however, by the increased PRA seen in patients with VAD support [54,55]. The results, as far as acute and chronic rejection in future transplant patients will be interesting to analyze.

In the adult population, improvements in VAD support has led to another dilemma, the potential misallocation of organs. Currently, many patients supported by an LVAD are clinically stable and discharged. They, however, are given 30 days of Status 1A time on the transplant list because of the historic risk of death with a device. Though they are clinically stable, they may receive a heart that could be better utilized in a patient who was not a candidate for VAD support [63]. This phenomenon could extend into the pediatric population as stability on VAD support improves.

Quality of life

Not surprisingly, children with CHD have a decreased quality of life (QoL) that correlates with the severity of the CHD, but interestingly, post-HT they continue to have a decreased QoL in the short-term [64,65]. However, evaluating adult patients who have undergone a pediatric HT at least 10 years prior, patients report minimal physical limitations and an equivalent QoL to healthy controls [2,66]. As a survival advantage has been established for the pediatric VAD, the implications on the quality of life (QoL) of these patients has been investigated. It is commonly accepted that a pediatric VAD provides an increased QoL when compared with ECMO. However, the QoL while supported with a pediatric VAD has not been reported. The adult population, however, has shown an increased QoL for patients with a VAD when compared with optimal medical management, further the QoL continues to increase as experience with devices, postoperative care and patient selection improves [67].

Though QoL while supported with a pediatric VAD has not been reported, the more important long-term QoL of patients after HT has been analyzed. Pediatric patients who require MCS and receive a VAD prior to HT have an equivalent QoL compared with patients who do not require MCS, as reported by their parents [68,69]. This is significant as the VAD group is a sicker group with a higher risk of complications, including neurological, and it correlates with the fact that patients who require VAD support prior to HT have similar cognitive outcomes to those not requiring MCS [70].

Cost

As with any emerging device, the VAD has been scrutinized for its expense. The cost of the adult VAD has been evaluated repeatedly and has shown a dramatic decrease in the cost per quality adjusted life year (QALY) gained from >US\$800,000 during the REMATCH era to closer to US\$200,000 currently for DT with some reporting much lower for BTT [71–73]. This reduction has been driven by improved survival, increasing QoL, improved postoperative care, decreased complications, improved patient selection and increased device durability. Initial analysis of cost–effectiveness of the pediatric VAD shows a cost/QALY gained of US\$120,000 [74]. While this is above the typically acceptable threshold of US\$100,000, it is substantially less than some other pediatric life sustaining therapies [75]. It does remain well above the US\$50,000/QALY gained for a HT [76].

Costs have been shown to be lower at higher volume institutions [77]. Overall, high costs in the pediatric population are partially driven by the increased necessity of biventricular support, inability to discharge a patient, lagging device development and frequent complications. With modification of some of these factors, it is possible that an increase in cost-effectiveness for pediatric VADs could not only mimic the increase seen with adult VADs, but surpass it. Pediatric post-HT patients have the potential for longer survival than their adult counterparts. Additionally, they will be surviving through higher quality of life years. As VAD outcomes improve and as survival and QoL after HT improves, the cost/QALY gained for a pediatric VAD could dramatically decrease.

Patient selection

Most consider timing and patient selection to be the most important factors impacting outcomes with pediatric VADs [17,33,78]. Certain higher-risk groups have been identified. Specifically, smaller patients have worse outcomes on VAD support. The reasons are likely multifactorial including increased likelihood of having a CHD diagnosis, having smaller anatomy and requiring a smaller device with lower flows and the frequency of postcardiotomy support [33]. Other factors that predict a worse outcome are end-organ dysfunction prior to VAD placement, renal and hepatic dysfunction, which could potentially be avoided with earlier VAD placement.

As VADs have proven safe and effective in adults there has been a noticeable 'downshifting' of risk, referring to the placement of VADs in patients who are not yet critically ill [79]. This is beginning to be mirrored in the pediatric population with the goal of improving preoperative status by avoiding patient physical debilitation as well as renal, hepatic and respiratory failure. This practice will improve the measured outcomes of VAD support not only by improving preoperative status, but the VAD will also be placed in less sick patients, a group which inherently possesses an improved survival. The alternative is the risk of VAD placement in patients who are too healthy, potentially exposing them to VAD-associated complications when HT would have occurred prior to any MCS requirement. The decision of when to place a VAD is difficult and should be decided individually based on the patient's estimated time spent on the waiting list, taking into account their size and PRA status, as well as their current health.

Conclusion

The VAD has proven itself superior in many situations as a bridge to transplant, though not without complications. As the survival advantage of the VAD as a BTT for pediatric heart failure has become accepted throughout the medical community, the views have shifted from previously considering ECMO and VAD as competing therapies to now accepting that these are unique therapies with different indications.

The VAD clearly has utility in the CHD population for both pediatrics and adults with CHD. It has been utilized successfully in SV patients and patients with a right systemic ventricle. It allows for a similar QoL after HT and has a reasonable cost profile. Unfortunately, the literature regarding VAD use in patients with CHD is severely lacking. Future

improvements in patient selection and timing will help improve outcomes, as will improvements in devices and postoperative care. As VAD design and postoperative care improves, it is not inconceivable that the survival rates with VAD support would rival that of HT, however, substantial strides must be made, even more so in the smallest of patients.

Future perspective

Studies

Patients with CHD represent a heterogeneous group. Therefore, the utility of any particular study to guide the pediatric or adult cardiac heart failure specialist is limited. The registry designed to collect data on MCS use in SV patients will help to address this issue. With this collection of a large population, more conclusive determinations can be made. Equally as important, individual subsets can be analyzed to find the most representative patient population to compare with each individual patient to more effectively guide treatment.

As more adults with CHD who have undergone complex surgical repairs reach their fourth decade of life, it is anticipated that many will ultimately develop heart failure that will eventually require transplant. Many of these patients may require VAD support as BTT or as DT, depending on their age and coexisting diagnoses. It will be imperative to collect and analyze this information as each patient will be unique in their original diagnosis, type of surgical repair and subsequent mechanism of heart failure.

Improved outcomes

Outcomes in pediatric VADs should be anticipated to improve as seen in the adult population. This will be driven by improved devices, increased experience with pediatric VADs, increased experience with each anatomical abnormality with CHD, improved postoperative care and discharging of patients. Long-term device durability has not traditionally been as important in the pediatric population because VADs are placed for BTT; however, with a few devices placed for DT, the longevity of these devices can be investigated. As experience increases the complication rate should continue to decrease. These factors will not only improve survival and QoL, but decrease costs. Future research should aim to guide decision making, specifically determining the timing of VAD placement as well as patients who should not receive a VAD.

Future devices

The PumpKIN trial was recently designed to evaluate the effectiveness of VADs in small children, specifically utilizing the Jarvik 2000 (Jarvik Heart Inc., NY, USA) (Figure 4) [80]. Another pediatric VAD that is currently under investigation is the PediaFlow (Pedia-flow ventricular assist device Consortium, PA, USA). Both are small axial flow devices aimed to support the smallest of patients. The VADs under development for the adult population are smaller than current adult devices and could potentially be utilized to support smaller patients than possible with the current adult devices. The HeartMate III (Thoratec Corp., CA, USA) (Figure 5A) is a continuous-flow VAD with a centrifugal design that may require only antiplatelet therapy for anticoagulation [81]. The HeartWare MVAD (Heartware Inc., MA, USA) (Figure 5B) is a very small axial flow device with the potential for placement

intraventricularly with the outflow cannula placed across the aortic valve [82]. The Synergy (CircuLite/Heart Ware, Inc., MA, USA) is a miniature pump designed to provide partial support to the adult and could potentially be utilized in pediatric patients (Figure 5C & D) [83].

Future device for single ventricle patients

An alternative strategy to support the pulmonary circulation of a failing Fontan has been proposed [84]. A cavopulmonary-assist device, technically not a VAD because it is not assisting a ventricle, placed percutaneously sits at the total cavopulmonary connection and pumps blood from the SVC and IVC into the pulmonary arteries avoiding the otherwise necessary step of taking down the Fontan [85]. It allows for increased oxygenation with an improved preload and cardiac output [86,87]. This device, currently early in its investigational stages, could be utilized in the pediatric or adult failing Fontan to allow the patient to recover to become a better transplant candidate.

VAD comparison group

The adult population has long recognized that VAD support leads to increased survival and QoL in patients in the advanced stages of heart failure. The devices, postoperative care and patient selection have improved significantly to provide an increase in survival. While the VAD does not yet offer a comparable long-term survival to HT, it is conceivable that future devices could offer the durability and decreased risk profile necessary for outcomes on VAD support to rival that of HT. The VAD has the additional advantage of not being limited to the number of donor hearts available.

With the existing data demonstrating the superiority of VAD support over ECMO in many situations, it is now accepted that these are not competing therapies, but different therapies with different indications. The comparison group for VAD support should soon transition from ECMO to HT; however, this may be difficult. The outcomes for pediatric HT vary with age and diagnosis, but overall are excellent with a median survival of 12–20 years [2]. This range of outcomes presents difficulties when comparing outcomes to VAD support. Further complicating this comparison, VAD support is utilized as a BTT, therefore the long-term outcomes for these two therapies are interdependent.

To achieve equivalent outcomes as pediatric HT, the pediatric VAD would require considerable improvements. The long-term durability of pediatric devices is largely unknown, though many larger pediatric patients are supported with adult devices with known excellent long-term durability [88]. The VAD would have to experience a significant reduction in adverse events, most notably CVEs, though with increased postoperative experience this is being accomplished [53]. Furthermore, the pediatric VAD has an additional technical complication, its inability to grow. The inability of the current adult VADs to support a low enough flow without pump thrombosis in combination with the upper limit of flow possible with pediatric devices would imply the necessity of reoperations if placed in any patient smaller than an adolescent. This could be overcome by devices that were able to support a wider range of flows or smaller devices with a narrow range that could be placed endovascularly across the aortic valve. While they would require exchange,

the morbidity of this procedure would conceivably be low. These advances would have to occur in a way that improves outcomes faster than advances in immunosuppression improves transplant outcomes. However, when considering that the adolescent survival after HT is similar to that of adults and that they are able to utilize adult devices, it does become plausible that these patients could, in the distant future, have equivalent survival with a VAD as DT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Executive summary

Overview of pediatric heart failure & transplantation

- Pediatric heart failure is a problem, with heart transplant (HT) as the best solution, unfortunately it is only available to a limited number of patients. Ventricular assist device (VADs) have emerged to fill this gap and bridge patients to transplant.
- Heart failure in patients with congenital heart disease (CHD) represents a unique population. Additional factors must be considered when evaluating these patients for VAD support.

Heart transplant

- Outcomes after transplant are excellent, but the success ranges widely based on age. Patients who undergo HT for heart failure secondary to CHD have a worse outcome.

Ventricular assist device

- These have shown utility in the adult population and have recently proven superior to extracorporeal membrane oxygenation (ECMO) in the pediatric population.

Available devices

- A description of different types of devices available including continuous-flow, pulsatile devices as well as devices intended for short-term support.

Indications for VAD

- VAD placement in the pediatric population is different than in adults, with the majority being placed as a bridge to transplant. Specifically in CHD patients, almost all will be placed anticipating later HT.

VAD in CHD

- Little data exist on this topic, what does exist shows it can be done successfully and for significant duration:
 - Single ventricle patients:
 - This represents a very difficult set of patients to treat. VAD has been utilized, though with worse survival than in patients with biventricle physiology.
 - Adults with surgically repaired CHD:
 - This is a growing population and each will be unique. Very little literature exists describing successful procedures in these patients.

VAD complications

- A description and estimation of incidence of common complications associated with pediatric VAD support.

Impact on transplant match

- As VAD use increases and allows for longer durations on the transplant list, there will be an increased recipient pool. Most anticipate this leading to longer waiting times.

Quality of life

- The quality of life with a VAD in the pediatric population is largely unknown. It is known, however, that if they live to transplant they have equivalent outcomes as those who did not require mechanical circulatory support.

Cost

- The current cost per Quality Adjusted Life Year gained estimate for a pediatric VAD over ECMO is US\$120,000. This is certainly expensive but not unreasonable.

Patient selection

- Patient selection and the timing of VAD placement will likely become the driving force when evaluating outcomes with VAD support. The decision is difficult and there is little research to help guide the decision.

Future considerations

- A description of future studies, devices and ways to improve outcomes of pediatric VADs.

VAD comparison group

- The pediatric VAD and ECMO are no longer valid comparison groups. The VAD has shown superiority in many situations. It should transition from having the survival and complications compared with ECMO to having them compared with HT, though, there will be some difficulties with this. While the VAD does not have the same increase in survival as HT, it is not inconceivable, that it will in the distant future.

Figure 1. Number of pediatric heart transplants per year and percentage for chronic heart disease

CHD: Congenital heart disease; OHT: Orthotopic heart transplant.

Data taken from [89].

Figure 2. Berlin EXCOR (Berlin Heart Inc., Berlin, Germany) sizes: 10, 25, 30, 50 and 60 ml
Reproduced with permission from Berlin Heart Inc.

Figure 3. Adult devices utilized in pediatric population
(A) HeartMate II (Berlin Heart Inc., Berlin, Germany)
(B) HeartWare HVAD (HeartWare Inc., MA, USA).
(A) Reproduced with permission from Berlin Heart Inc.;
(B) reproduced with permission from Heartware Inc.

Figure 4. Pediatric Jarvik 2000 (Jarvik Heart Inc., NY, USA)
Reproduced with permission from Jarvik Heart Inc.

Figure 5. Devices under investigation, not for clinical use. Images printed with permission from each manufacturer
(A) HeartMate III (Thoratec Corp., CA, USA). **(B)** HeartWare MVAD (left) with HVAD (right) for size comparison (Heartware Inc., MA, USA). **(C)** Synergy (CircuLite/HeartWare, Inc., MA, USA) implanted. **(D)** Synergy pump the size of an AA battery.
(A) Reproduced with permission from Thoratec Corp.; **(B)** reproduced with permission from HeartWare Inc.; **(C & D)** reproduced with permission from CircuLite/HeartWare, Inc.

Table 1

Studies evaluating ventricular assist device use for pediatric end-stage heart failure[†].

Study (year)	Patients (n)	Device	Mean/median duration (days)	Survival to transplant/recovery/waiting (%)	Ref.
Blume <i>et al.</i> (2006)	99 [‡]	Multiple	57	83	[14]
Inamura <i>et al.</i> (2009)	21	EXCOR	42	86	[11]
Miera <i>et al.</i> (2011)	7	HeartWare HVAD	75	100	[15]
Morales <i>et al.</i> (2011)	73	EXCOR	52	77	[10]
Moreno <i>et al.</i> (2011)	12	EXCOR	73	75	[18]
Chen <i>et al.</i> (2012)	37 [†]	Multiple	77	86	[9]
Almond <i>et al.</i> (2013)	204	EXCOR	40	75	[12]
Cabrera <i>et al.</i> (2013)	28	HeartMate II	324	96	[16]
Cassidy J <i>et al.</i> (2013)	102	EXCOR	39	84	[13]

[†] Some studies may overlap as some are based on multicenter databases.

[‡] Studies contain 26 and 5 short-term devices.