



Pediatric ventricular assist device registries: update and perspectives in the era of miniaturized continuous-flow pumps

Kevin M. Lichtenstein¹, Hari P. Tunuguntla², David M. Peng³, Holger Buchholz¹, Jennifer Conway⁴

¹Department of Cardiothoracic Surgery, Stollery Children's Hospital, University of Alberta, Edmonton, Alberta, Canada; ²Department of Pediatrics, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas, USA; ³Department of Pediatrics, Mott Children's Hospital, University of Michigan, Ann Arbor, Michigan, USA; ⁴Division of Pediatric Cardiology, Department of Pediatrics, Stollery Children's Hospital, University of Alberta, Edmonton, Alberta, Canada

Correspondence to: Jennifer Conway, MD. Division of Pediatric Cardiology, Department of Pediatrics, Stollery Children's Hospital, 8440 112 Street NW, Edmonton, Alberta, T6G 2B7, Canada. Email: jennifer.conway2@albertahealthservices.ca.

The success of ventricular assist devices (VADs) in the treatment of end-stage heart failure in the adult population has led to industrial innovation in VAD design, focusing on miniaturization and the reduction of complications. A byproduct of these innovations was that newer generation devices could have clinical applications in the pediatric population. Over the last decade, VAD usage in the pediatric population has increased dramatically, and the newer generation continuous flow (CF) devices have begun to supplant the older, pulsatile flow (PF) devices, formerly the sole option for ventricular assist in the pediatric population. However, despite the increase in VAD implants in the pediatric population, patient numbers remain low, and the need to share data between pediatric VAD centers has become that much more important for the continued growth of VAD programs worldwide. The creation of pediatric VAD registries, such as the Pediatric Registry for Mechanical Circulatory Support (PediMACS), the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) and the Advanced Cardiac Therapies Improving Outcomes Network (ACTION) has enabled the collection of aggregate data from VAD centers worldwide, and provides a valuable resource for clinicians and programs, as more and more pediatric heart failure patients are considered candidates for VAD therapy.

Keywords: Pediatrics; ventricular assist device (VAD); continuous-flow



Submitted Sep 28, 2020. Accepted for publication Jan 18, 2021.

doi: [10.21037/acs-2020-cfmcs-18](https://doi.org/10.21037/acs-2020-cfmcs-18)

View this article at: <http://dx.doi.org/10.21037/acs-2020-cfmcs-18>

Introduction

In the adult population, mechanical circulatory support (MCS) is now a major modality for the treatment of patients with end-stage heart failure (1,2). With the improved experience and success of ventricular assist devices (VADs) in the adult population, adoption and adaptation of these technologies for use in the pediatric population was the natural next step. The increased use of VADs in children parallels the known risk of heart failure in children. Hospital admission with heart failure increases the risk of death in children by twenty-fold, with an overall mortality rate of 7–11%, while the cardiac transplant waitlist

mortality ranges from 5–39%, depending on age, diagnosis and other recipient factors. The International Society for Heart and Lung Transplantation (ISHLT) Pediatric Heart Failure Registry showed that of pediatric patients admitted to hospital for their first presentation of heart failure, 28% were transplanted, 16% received a VAD, 13% were awaiting transplantation and 11% died (3). It is clear then that end-stage refractory heart failure is associated with high morbidity and mortality in the pediatric population (4–6).

In the last decade, end-stage heart failure management in pediatrics has improved dramatically with the increased use of VADs. Currently, over a third of pediatric transplant recipients are bridged to transplantation on a VAD

(7,8). Previously, strategies for mechanical support in the pediatric population were limited to veno-arterial extracorporeal membrane oxygenation (VA-ECMO), or paracorporeal pulsatile flow ventricular assist devices (PP-VAD) (1,9). PF-VADs provide superior support for a longer duration compared to extracorporeal life support (ECLS), but complication rates historically have remained high (9). In recent years there has been a transition away from ECLS towards the use of VADs in the pediatric population, as VADs can provide long-term stabilization of patients waitlisted for transplantation, allowing for nutritional and physical rehabilitation (2,4,10). As VAD adoption for pediatric heart failure has increased, mortality has subsequently decreased, with one study finding that waitlist mortality has reduced by half since the introduction of VAD support (11).

Until recently, when long-term mechanical support was required in pediatric patients, the chosen modality was the PP-VAD system (7). While these devices are still being used, there has been increased use of both short-term and long-term continuous flow VADs (CF-VAD) (12). This increase stems from a trend observed in adults where VAD technology was transitioned from pulsatile flow VADs to CF-VADs due to improved survival and decreased adverse events. This created an opportunity for adoption of long-term CF-VAD systems in pediatric patients, as miniaturization has made the device profiles more suitable for pediatric implantation. The majority of long-term CF-VADs in the pediatric population are implanted for cardiomyopathy, but usage in the congenital heart disease (CHD) population, particularly in complex congenital patients, is increasing (7,13,14).

Numerous single center studies have been published outlining center focused-experience with CF-VADs in pediatric populations. Outcome data on survival, transplantation, discharge and complication rates are now widely available, but center-specific results are limited by the small patient numbers and the variation in practice across centers. With the increasing adoption of CF-VADs in the pediatric population but lower volumes of patients per center, a need quickly arose for practitioners to closely monitor and follow their pediatric VAD patients, collect common data points and share this data between centers through registries (4). Registries that collect aggregate data from numerous centers now exist and provide benefit to practitioners and pediatric VAD patients by producing a larger sample for analysis of outcomes and experience. This should allow for the modification and overall improvement

in center-specific management of this challenging, complex and rare patient population, and alleviate the steep learning curve inherent when starting a new pediatric VAD program (14). This review will highlight the findings from the individual registries on CF-VADs, with an emphasis on long-term devices.

Ventricular assist device registries

PediMACS

PediMACS, the pediatric registry for mechanical circulatory support in North America, was created in 2012 and collects prospective data from pediatric VAD patients aged less than nineteen years of age (12). Data collection fields are representative of the variation present in the pediatric VAD population, including patient size, anatomy, type of device and indication for device implant (12). The value of PediMACS is that it is a large data registry from which outcome data can be derived for devices, the majority of which are not FDA approved for pediatric use (12). Without a registry like PediMACS, centers would have to rely on their own limited experience. In a recent analysis of PediMACS, over 40% of centers implanted only one device over a three-year period (9). The aggregation of multicenter data collected by PediMACS is an invaluable resource for all programs.

The most recent PediMACS annual report highlights the value this registry provides, as it outlines some of the major conclusions gained from examining the data collected since the registry's inception (12). PediMACS includes close to 600 patients with over 750 implanted devices and includes patients <1 year of age (21%), one to five years of age (19%), six to ten years of age (17%) and eleven to nineteen years of age (43%) (12). The majority of the patients in the registry have cardiomyopathies (61%), with the remainder having myocarditis (11%) and CHD (20%) (12). Of the CF devices used, intracorporeal continuous (IC) flow devices were the most common (47%), with paracorporeal devices only being used in 19% of patients (12). Paracorporeal devices (both continuous and pulsatile) were more commonly used in younger and smaller patients compared to IC devices (12). Of the paracorporeal continuous (PC) flow devices implanted, 49% of patients were INTERMACS profile 1, and of these, 38% had diagnoses of CHD. This is compared to 19% INTERMAC profile 1 IC implantations, of which 11% were CHD patients (12). Patients with IC devices also had better renal function, were less likely to have had a previous cardiac operation and were less likely to be tube

fed prior to implantation (12). This data demonstrates that there is a marked difference in patient profiles across devices, not only based on size and age, but also pre-implant clinical characteristics. Based in competing outcomes at six months, a positive outcome (transplant, recovery or alive on device) was seen in 92% of patients in the IC device cohort and 63% in the PC device cohort (12). In the IC group, over one third (34%) of patients were still supported on a device at six months, and one fifth (20%) were still device-supported at one year (12). Further, more than 50% of patients implanted with an IC device were designated as a bridge to candidacy, demonstrating an overall increased comfort level in having these patients on support in the long term with less rush to transplant (12). This trend indicates that centers with IC device experience are increasingly comfortable following and caring for long-term VAD patients (12). The PediMACS experience showed that 59% of patients were discharged with a IC device; however, discharge was not as frequent in patients that weighed <20 (12). As seen in the adult literature, complication rates with the IC devices are improved compared to PC and PP devices. IC device patients had a longer period before first neurologic event and stroke (12). The only factor found to increase the risk of death in the IC patients was the need for ECMO support prior to implantation (12).

For the PC group, the analysis of the PediMACS registry showed that over one third of patients were transplanted within six months of implantation (12). As for PC device patients, history of previous valve operations, severe right heart failure (RHF) and blood type O were associated with increased mortality (12). Overall, analysis of data from the PediMACS registry regarding continuous flow devices demonstrates that IC device patients are generally less sick, older and with fewer congenital diagnoses compared to PP or PC device patients (12). PC device are now being used in patients who would normally be treated with PF devices as a bridge to transplantation, like those with single-ventricle physiologies, those weighing <5 kg and those with co-morbidities (12). The overarching theme from the most recent PediMACS registry analysis is that IC VADs have quickly become the most common form of mechanical circulatory support (MCS) in the pediatric population in older children, and the favorable outcomes of patients on these devices imply that this trend will continue.

Pedi-EUROMACS

The European Registry for Patients with Mechanical

Circulatory Support (EUROMACS) is a registry that collects data on both adult and pediatric patients on MCS across Europe (15). Within EUROMACS, a pediatric subcommittee advises and evaluates all clinical data collected from the pediatric population on MCS to aid in understanding and monitoring of the clinical course of the pediatric subset (15). Since EUROMACS collects data from children and adults, pediatric patients can be followed into adulthood (>19 years of age) (15). Conveniently, outcomes are structured so that they are comparable with experience derived from the PEDIMACS registry, allowing for direct comparison between European and North American outcomes in pediatric MCS patients (15). In their second report, Pedi-EUROMACS outlined their outcomes since inception (15). A total of 353 patients with 398 device implants were included in the most recent analysis (15). Ages of patients ranged from zero to nineteen years of age with 15.6% of patients under the age of one (15). CF-VADs made up just under 50% of the total devices implanted (15). Among CF-VADs patients, 4.8% were implanted with a HeartMate II® (HMII), while 3.7% received a HeartMate 3® (HM3) and 31.7% were implanted with a HeartWare HVAD® (15). In total, 136 patients, aged one to nineteen years, were implanted with CF-LVADs alone (15). Seven patients were implanted with a CF-LVAD plus a CF-RVAD and three received CF-BiVAD support (15). One key finding relevant to the current review was that survival in patients >10 kg was not significantly different between paracorporeal (continuous and pulsatile) and IC devices, indicating that perhaps the type of VAD is not a major risk factor for worse outcomes, and perhaps patient characteristics may play more of a significant role, as patients with a BSA <1 m² had higher mortality than patients with a BSA >1 m², regardless of flow type (15). An additional study of long-term CF-VAD using the EUROMACS registry found that the mean support time of IC CF-VAD was 8.4 months, which is much longer than that of the PediMACS experience (10). At 12 month follow-up, 89% of patients implanted with long-term CF-VAD from January 2009 to June 2016 had a positive outcome (transplanted, were on support or had been weaned from the device) (10).

ACTION

Advanced Cardiac Therapies Improving Outcomes Network (ACTION) is a multi-center learning health system focused on improving pediatric heart failure through active collaboration and data sharing. While ACTION does

have a registry component, its primary focus is on quality improvement initiatives (4). Utilizing the ACTION, a recent study outlined outcomes in 35 pediatric and adult congenital patients implanted with the HM3 (16). The majority of the patients were pediatrics (80%). The median weight was 65.7 kg, with a range of 19.1 to 114.1 kg (16). The majority (63%) of these patients had a diagnosis of dilated cardiomyopathy, and 17% had CHD (16). Of those with a CHD diagnosis, Fontan circulation patients made up 83% (16). Bridge to transplantation was the most common indication for implantation (54%) with destination therapy making up 11% of the cohort and bridge to recovery patients making up only 6% of the cohort (16). After HM3 implant, the median length of hospital stay to discharge or transplant was 29.5 days for the entire study population (16). In this study, 57% of the entire group was discharged from the hospital with HM3, with an overall mortality of 3% (16). In this cohort there were fourteen patients <60 kg with eleven undergoing transplant and no deaths at the end of the study. This data, despite being drawn from a relatively small number of patients compared to adult studies, shows that one benefit of multi-center collaboration is the ability to rapidly provide insight into patient outcomes, specifically when patient volumes are too small at any one center to enable this type of analysis. This study also provided the first evidence that HM3 could be utilized effectively in pediatric patients.

Short-term continuous flow VADs (STCF-VAD) in the pediatric population

Prior to the adoption of STCF-VADs for support in the pediatric population, ECLS was favored for short-term mechanical support. Recently however, STCF-VAD support usage has been steadily increasing in the pediatric population (17). Due to the increasing confidence with short-term CF-VAD support, more centers have lowered their thresholds for instituting CF-VAD support in critically ill pediatric patients (13). Using different pumps, configurations and cannulation approaches, the STCF-VAD can be used to support either the left or right ventricle (17). Devices currently reported to be used in pediatrics for STCF-VAD management include the Centrimag (Abbott, Chicago, IL, USA), the Pedimag (Abbott, Chicago, IL, USA) and the Rotaflow (Maquet, Rastatt, Germany) system, as well as the TandemHeart, Abiomed Impella and AB500 (17,18). The Centrimag/Pedimag system utilizes a magnetically levitated pump head, potentially reducing

the risk of thrombus formation within the pump, while the Rotaflow pump has a single monopivot bearing with magnetic suspension (17). When compared to ECLS from a rehabilitation standpoint, STCF-VAD support allows for cannulation approaches that permit patients to be mobilized while still maintaining the possibility for easier transition to the Berlin Heart PP-VAD system (17). A single center study examining pediatric patients supported by STCF-VAD showed that the use of STCF-VADs allowed time for cardiac recovery as well as improved assessment and recovery of multi-organ system function (17). STCF-VAD usage in this cohort supported 67% of the patients to discharge and duration of support lasted a median of eleven days. The longest duration of support lasted seventy-five days, with 58% of patients transplanted, 14% recovered and 28% died (17). Complications included infection (22% of patients) and non-neurologic ischemic events (11% of patients) (17). The conclusion from this study was that STCF-VADs were a useful tool for bridging pediatric patients to recovery, transplant or a longer term device (17). The findings of the study also demonstrated the superiority of CF-VAD support in the short-term over ECMO support (13). This is likely due to the improved LV decompression gained from CF-VAD support when compared to ECMO (13). A recent study of PediMACS pediatric patients requiring STCF-VAD support validated the above points. The most common diagnoses requiring short-term support were cardiomyopathy (40%), CHD (41%) and myocarditis or transplant rejection (19%) (18). Support strategy at time of implantation was either bridge to transplantation (40%), bridge to candidacy (25%) or bridge to recovery (29%), with only 6% of patients on short-term support as a rescue strategy (18). In terms of duration of support, the median length of support was fifteen days, and was shortest (median six days) in the bridge to recovery group compared to the bridge to long-term device group (median fourteen days) and the bridge to transplantation group (median forty-seven days) (18). Only 8% of patients in this study required support for more than three months (18). The proportion of patients with infections on STCF-VAD in this study was 17%, with bleeding seen in 28.6% of patients and neurologic dysfunction seen in 24%. Of the neurologic events, 47% were ischemic or hemorrhagic CVAs (18). Overall, positive outcomes occurred in 71% of patients requiring ST-CF VAD support, with 17% eventually being transplanted, 30% eventually recovering and 22% requiring transition to a longer-term device.

Long-term continuous flow VADs in the pediatric population

The three long term IC CF-VADs currently being used in increasing numbers in the pediatric population are the HeartMate II® (Abbott, Chicago, IL, USA), HeartMate 3® (Abbott, Chicago, IL, USA) and HeartWare HVAD® (Medtronic, Minneapolis, MN, USA) (7,13). Initially designed for the adult population, these devices have a profile diminutive enough to be suitable for implantation in pediatric patients of appropriate size; however, none of these devices are currently FDA approved for use in the pediatric population (7,9). In contrast to the adult population, the majority of pediatric patients implanted with a long-term CF-VAD are INTERMACS profiles 1 or 2, and the most common support strategy at implantation is typically bridge to transplant (54%), followed by bridge to candidacy (40%) and destination therapy (6%) (9). For these reasons, many centers worldwide have utilized these systems in pediatric patients due to their more favorable characteristics and the opportunity for these patients to eventually be discharged (9,13). At six months, 92% of patients in one study had a positive outcome, with 61% receiving transplants and 31% stable on the original CF-VAD (9). One of the most important benefits of intracorporeal CF-VAD in the pediatric population is that discharge from hospital is a possible outcome (9). In the same study, about half of the patients included were successfully discharged home with a CF-VAD (9). While the above devices have been designed initially for adults, there is a prospective, multi-center, single arm feasibility study evaluating the clinical feasibility and safety of the Jarvik 2015, a miniaturized, fully implantable continuous flow VAD (19,20).

HeartMate II

The HeartMate II (HMII) is an axial continuous-flow pump that has been extensively studied in the adult population (21). This device is capable of generating up to 10 L/min of flow by utilizing a mechanical-bearing supported internal impeller design and inflow cannula that is separate from the pump housing. This second generation VAD reduced the number of components compared to first generation pumps, while achieving higher speeds (up to 15,000 rotations per minute), all within a more compact package with extended battery life of up to ten hours (22,23). Although the HMII was smaller in size compared to first generation VADs such

as the HeartMate XVE (22,23), the HMII is still of a sizeable profile that it requires intra-abdominal implantation (21). Due to this larger size, the HMII was initially adopted for use in larger pediatric patients, most notably adolescents with a body surface area (BSA) ≥ 1.3 m². A larger BSA allows for optimal inflow cannula positioning parallel to the interventricular septum towards the center of the LV cavity (13,23). Overall, outcomes in patients implanted with HMII were excellent, with a >90% bridge to transplant rate (13). This resulted in a reduction in the use of 50 and 60 mL Berlin EXCOR pulsatile pumps (13). With the introduction of the smaller profile, newer generation devices, pediatric VAD centers have shifted their attention rapidly to the HeartWare HVAD® and the HeartMate 3®.

HeartWare HVAD

The Heartware HVAD has been the most frequently implanted device in the pediatric population (13). The HVAD, a hydrodynamic centrifugal flow pump with a reduced friction design, and a displaced volume of 45 mL, can provide flows of up to 10 L/min (22,23). The size of the HVAD device allows for easier implantation within the pericardium in smaller children. The reduction of both the device housing size and the inflow cannula size has been thought to help reduce hemolysis and improve pump efficiency (22,23). The second and third generation VADs (HVAD, HM3) also allow for insertion of the inflow cannula at the ventricular apex, parallel to the interventricular septum, as opposed to atrial placement (22,23). The apical and parallel location of the inflow cannula reduces the risk of ventricular suction events and blood stasis (22,23).

Numerous single center reports have found that HVAD usage in the pediatric population could be successful (7,14,24). Following the successes reported by single centers, multi-center collaborative reports followed suit. The largest international pediatric experience with the HVAD was Conway *et al.* [2018], which included 200 patients from thirty-four sites in twelve different countries (7). The majority of patients implanted with an HVAD had cardiomyopathy (79%), while 14% were CHD patients, of which the majority (62%) had a biventricular circulation (7). The median duration of VAD support in these patients was 86 days, with the longest length of support stretching to 1,642 days (7). By one year post-implant, 65% had undergone transplantation, 3.2% had achieved recovery to explant and 20.8% remained on the device (7). Mortality

was 9.9% at six months and 10.7% at twelve months, with the majority of deaths occurring in first three months post-implant (7). The only significant factor found to be associated with mortality was the need for temporary RVAD support post-implant (7). At 120 days, 55% of patients survived to discharge (7). The authors also found that although there were fewer discharges in the group where BSA was $\leq 1 \text{ m}^2$ compared to those in the larger BSA group, this difference was not statistically significant (7). Overall, this multi-center study demonstrated that the size and profile of the HVAD system make it suitable for implantation in the pediatric population, with good intermediate-term results, including the possibility for discharge home and long-term out of hospital care for pediatric patients suffering from end-stage heart failure. The PediMACS registry reports, outlined previously, have improved the quality of statistical outcome data for pediatric HVAD patients and have shed light on the adverse event profile. Analysis of data from the PediMACS registry is producing a more comprehensive understanding of how pediatric patients with an HVAD fare clinically in the short, medium and long-term.

HeartMate 3

The HeartMate 3 (HM3), a magnetically levitated centrifugal pump, is currently FDA approved for application in end-stage heart failure patients with a BSA $> 1.5 \text{ m}^2$ as a bridge to transplant or destination therapy pathway (16,23). HM3 has a larger profile than the HVAD (22,23). Furthermore, its usage of a magnetically levitated rotor is the main design innovation that has been attributed to the reduction of complication rates compared to those of the HMII (22). The MOMENTUM 3 trial demonstrated that the centrifugal flow HM3 has a lower complication rate, with respect to thromboemboli and hemorrhage, than the axial flow HMII, with a two-year survival in the adult population of 80% (21,25). Due to its design, the HM3 has a larger profile than the HVAD, making implantation in smaller children more challenging (16). Conversely, the design of the inflow cannula on the HM3, with its shorter profile may lend itself better to utilization in smaller hearts, when compared to HVAD or HMII (16). Challenges aside, HM3 usage in pediatric patients as a long-term IC CF-VAD is increasing with the above mentioned registries well positioned to provide further information on outcomes (16).

Continuous flow VADs in the complex CHD population

CHD is the most common diagnosis in pediatric patients hospitalized for heart failure (14). Pediatric CHD patients have a high lifetime risk of heart failure with an estimated 10–20% of patients requiring a heart transplant (14,26). Unfortunately, waitlist mortality is also higher in the CHD population (14). A solution to bridge these patients to transplant was needed to reduce waitlist mortality, and VADs have been used for this strategy with steadily increasing usage but variable success (14). In a 2018 analysis, 25% of patients requiring mechanical ventricular support had a CHD diagnosis compared to the previous PediMACs report from 2016 where 16–17.5% of VAD patients had CHD (24,26). The most recent PediMACS report from 2019 found that of the 86 CHD patients, 29% were supported on a PP device, 34% were on a PC device while 26.7% were on IC CF-VAD support (12). Overall CHD patients requiring VAD are more likely to be younger, smaller and have had previous cardiac surgery compared to non-CHD patients (14). PC VAD usage has been demonstrated to be greater in the CHD population compared to non-CHD patients (36.1% *vs.* 12.9%), but survival outcomes were not found to be different. In addition, CHD patients were less likely to receive an IC VAD when compared to non-CHD patients (27.8% *vs.* 55.0%), with similar survival (14). When compared to the continuous flow devices, implantation of a PP device was associated with worse outcomes in patients with CHD compared to those with other diagnoses.

Among CHD patients who may benefit from VAD support, patients with single ventricle circulation pose the biggest challenge (13,14). The use of CF-VAD support in the single ventricle population may be limited to short term PC VADs in younger patients who are too small to receive an IC VAD (14). In older single ventricle patients with failing Fontan circulation, mechanical support with an implantable CF-VAD can allow for optimal hemodynamic support and discharge from the hospital while awaiting transplantation (13). Recent data suggests that CF-VADs may outperform PP-VADs in the single ventricle CHD population (13). It has been proposed that when compared to a pulsatile pump, the continuous decompression of the failing ventricle provided by the CF-VAD is superior due to the continuous pulmonary venous decompression, which creates a more optimal pulmonary circulation. At time of VAD implant, when compared to all the CHD patients

requiring VAD support, the single ventricle patients were the youngest and smallest, and more likely to receive a PC device (14). The data suggests some trends to account for this; Stage 1 single ventricle patients are typically under one year of age (73.9%), have low BSAs ($0.3 \text{ m}^2 \pm 0.2$) and are more likely to be in cardiogenic shock at time of VAD implantation (59.1%). The reasons leading to a higher proportion of single ventricle patients implanted with a PC device (78.3%) when compared to a biventricular patient may stem from the urgency of the implantation and the previous reported outcomes with pulsatile flow (14). While other device strategies may be considered in certain CHDs, the strategies are rare, with only two patients implanted with a total artificial heart and three patients with a percutaneous device in the most recent report dedicated to CHD (14).

In all pediatric VAD patients, PediMACS analysis demonstrates that CHD is a risk factor for mortality at six months, regardless of VAD type (36.4% *vs.* 12.1%) and CHD patients are also less likely to receive cardiac transplantation (29.1% *vs.* 59.9%) (14). Survival in CHD VAD patients is improved if they are implanted, at a high-volume center (≥ 15 patients per year), with an IC VAD, likely reflecting the differences in patient characteristics (14).

Complications of long-term continuous flow VADs

One of the main benefits of implanting a long-term device in a pediatric patient is the ability to discharge the patient home. This is beneficial not only because it allows for physical, nutritional and emotional rehabilitation, but also allows the child to return home with their family. However, even when a patient is well enough to be discharged home, long-term CF-VADs still carry risks of complications (27). The most common complications associated with long-term IC VADs in the pediatric population are bleeding, stroke, infection, pump thrombosis, pump malfunction and RHF (27). The following will summarize what is known about these complications for long-term CF-VADs.

Bleeding

Bleeding is a common complication that is reported after implantation of long-term CF-VADs. This is more commonly an early complication with the PediMACS registry reporting 21–28% of patients having bleeding within three months of implant, and this number decreasing to 5.5–8% at ≥ 3 months after implant (9,12,28). Bleeding

was also the most common complication in a multi-center study with 24% of pediatric HVAD patients experiencing a bleeding event (7). In a smaller study, specifically looking at centers in the ACTION network that have implanted HM3, 11.4% of patients had a bleed, with 2.9% of these bleeds being gastrointestinal (16). Analysis of EUROMACS data showed 5.9% of deaths were caused by major bleeding, however this data accounts for all VAD types, not just long-term CF-VADs (15).

Cerebrovascular accident (CVA)

CVAs are one of the most significant complications following long-term CF-VAD implant, with the majority of events occurring early after implant (29). Single center analyses have shown that CVA rates vary between centers. The PediMACS analysis of long-term CF-VAD patients, suggests that CVA occurs in 8% of patients within three months of implantation and falls rapidly to 1.8–4% after three months (9,12). Conway *et al.* [2018] found that 18% of CF-VAD patients implanted with the HVAD device suffered a neurologic event (7). Another study of HVAD in pediatric patients found a CVA rate of 10–12%, while a study of pediatric patients implanted with the HM3 device and followed over two years demonstrated no hemorrhagic or ischemic strokes in their patient group; but this study group included young adults (<30 years of age) (16,28). Finally, a study looking at complications, specifically stroke, in CF-VAD patients had a 6% mortality associated with CVA (10).

Cerebrovascular pathology secondary to long-term CF-VAD remains a major source of morbidity and mortality in this patient population, emphasizing the importance of meticulous maintenance of therapeutic anti-coagulation, blood pressure control and thorough patient support in and out of hospital.

Infection

Due to the nature of some IC VAD components transitioning from inside the body to outside, IC VAD use comes with an inherent risk of infection, and infections are one of the most common complications in pediatric CF-VAD patients. The PediMACS registry found that infections occurred in 25.7% of CF-VAD patients within three months of implant, and 11% of patients after three months or more (9). Conway *et al.* [2018] found that 15% of patients in their study with long-term CF-VADs had

a confirmed infection associated with their HVAD, while Pac *et al.* [2018] found an infection rate of 11.7% (7,30). When driveline infections (DLI) were examined in pediatric patients implanted with the HVAD system, 14.2% of patients were found to have a DLI (30). A study of pediatric patients implanted with HM3 found that 11% of patients experienced DLI (16). Infections have been associated with the need for re-hospitalization (16) and mortality in the CF-VAD population (10,27). While the EUROMACS registry has not specifically analyzed the data for long term CF-VADs, it has reported that approximately 6% of deaths in VAD patients are due to infection (15).

Overall, looking at all the data from the registries and single center studies, it appears that with CF-VADs, the infection rate lies somewhere between 10–15% and that infection can lead to significant morbidity and mortality in this patient population.

Pump thrombosis/pump exchange

In the pediatric CF-VAD population, pump thrombosis is a rare complication that can occur in newer generation CF-VADs, but at a much less frequent rate than PF-VADs. Pump thrombosis for IC CF-VADs in pediatrics also differs significantly from PC VAD pump thrombosis, as IC CF-VADs suspected thrombus is harder to visualize and pump exchange is a much more invasive procedure. One study analyzing the PediMACS data on CF-VADs had a device malfunction rate (which includes pump thrombosis) of 5.5% within three months of implantation and 9.2% in three or more months after implantation (9). VanderPluym *et al.* [2019] found a device malfunction/pump thrombosis rate of 7% in the early period (<3 months) and 5% in the later period in their study of HVAD in pediatric patients (28). In a combined study of HMII and HVAD pediatric patients, readmission for suspected pump thrombosis made up only 17% of total VAD patients (27). Of those suspected thromboses, 63% were confirmed to have a true pump thrombosis (27). All of the confirmed thromboses occurred in patients implanted with an HMII device (27). In a recent study of pediatric patients implanted with the HM3 device, there were no episodes of pump thrombosis, which is similar to what is reported in the adult population (27). Similarly, there were no episodes of pump malfunction, and no incidents where pump exchange was required (16).

Finally, pump thrombosis can lead to morbidity in the form of stroke. One study found that 50% of patients who suffered from an ischemic or hemorrhagic stroke had been

treated for pump thrombosis previously (29). This finding was also noted in another study of stroke rates in CF-VADs, with 75% of patients suffering a CVA having been previously treated for pump thrombosis (10).

Right heart failure

An analysis of the PediMACS registry specific to RHF found that 4.4% of patients initially implanted with an LVAD eventually required an RVAD (31). RVAD risk was decreased in patients that were older, had higher BSA and weighed more pre-implant (31). Furthermore, CF-VAD patients had a lower risk of RHF than PF-VAD (31). This is a common trend in pediatric VAD patients as candidates for CF-VADs are typically, larger, older and less complex than their PF-VAD counterparts who are more likely to be critically ill (31). In comparison, EUROMACS registry analysis found a RHF rate of 1.5% among all their VAD patients (15). In a study of HM3 in pediatric patients, the RHF rate was 20% and another study of CF-VAD complications found a 4% mortality associated with RV failure (10,16). The rates of RV failure requiring RVAD have been found to range from 6% to 10% (7,10). Conway *et al.* [2018] found that although RVAD or BiVAD support was rare, the introduction of an RVAD was associated with a four-fold increase in mortality (7).

Despite improvements in VAD technology and the increasing familiarity with pediatric VAD patients, complications do still occur in the pediatric population. The rate of complications and how to effectively manage VAD associated complications emphasizes the need to share experiences across centers. As the population of pediatric VAD patients continues to increase, these patients will require improvements to their outpatient care regimens, as the majority of these complications will occur post-discharge (27).

Conclusions

The use of CF-VADs is increasing in the pediatric population. Short term PC VADs allow for emergent left-heart support in the post-operative and critically ill pediatric population, especially those with potential for recovery and those with BSAs that prohibit the use of IC devices. CF-VAD usage has started to overtake ECMO as the standard of care in pediatric patients needing short-term MCS. As patient size and required duration of support increases, the use of IC VADs has become an

excellent option in these pediatric patients. This has seen the reduction of pulsatile pumps being used in bigger and older children as reflected by the demographics reported in the various registry reports. Numerous devices extensively studied in the adult population are being adopted for use in the pediatric population, with comparable outcomes and complication rates. They also yield the added benefit of potential discharge home. However, a major impediment to progress in pediatric VADs is that from center to center, patient volumes remain low. This leads to a steep learning curve for individual centers. Pediatric VAD registries and quality improvement networks are an invaluable tool as they provide outcome data and learning tools that smaller, lower volume centers can readily access to improve practice. With the rapid adoption of short-term and long-term CF-VADs, combined with the useful analytics provided by pediatric VAD registries, greater collaboration through the sharing of data via the aforementioned registries will create a larger sample pool from which more robust clinical data can be extracted and analyzed. As shown already, the number of pediatric cardiac patients who will require VAD support is likely to increase, and through established registries and learning networks the field can work together to improve outcomes in this unique patient population.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: JC: Unrestricted education grant from Abbott. The other authors have no conflicts of interest to declare.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Bartoli CR, Koenig SC, Ionan C, et al. Extracorporeal membrane oxygenation versus counterpulsatile, pulsatile and continuous left ventricular unloading for pediatric mechanical circulatory support. *Pediatr Crit Care Med* 2013;14:e424-37.
2. Conway J, Tunuguntla H. Big devices in small patients: adapting adult ventricular assist device for children. *J Heart Lung Transplant* 2020;39:580-1.
3. Dipchand AI, Zuckerman W, Auerbach S, et al. The first analysis of the international pediatric heart failure registry (iPHFR) – Heart failure hospitalizations. *J Heart Lung Transplant* 2018;37:S158.
4. Lorts A, Smyth L, Gajarski RJ, et al. The creation of a pediatric health care learning network: The ACTION quality improvement collaborative. *ASAIO J* 2020;66:441-6.
5. Dipchand AI. Current state of pediatric cardiac transplantation. *Ann Cardiothorac Surg* 2018;7:31-55.
6. Rossano JW, Shaddy RE. Heart failure in children: etiology and treatment. *J Pediatr* 2014;165:228-33.
7. Conway J, Miera O, Adachi I, et al. Worldwide experience of a durable centrifugal flow pump in pediatric patients. *Semin Thorac Cardiovasc Surg* 2018;30:327-35.
8. Rossano JW, Cherikh WS, Chambers DC, et al. The International thoracic organ transplant registry of the international society for heart and lung transplantation: twenty-first pediatric heart transplantation report-2018; focus theme: multiorgan transplantation. *J Heart Lung Transplant* 2018;37:1184-95.
9. Rossano JW, Lorts A, VanderPluym CJ, et al. Outcomes of pediatric patients supported with continuous-flow ventricular assist devices: a report from the pediatric interagency for mechanical circulatory support (PediMACS). *J Heart Lung Transplant* 2016;35:585-90.
10. Schweiger M, Miera O, de By TMMH, et al. Cerebral strokes in children on the intracorporeal ventricular assist devices: analysis of the EUROMACS registry. *Eur J Cardiothorac Surg* 2018;53:416-21.
11. Zafar F, Castleberry C, Khan MS, et al. Pediatric heart transplant waiting list mortality in the era of ventricular assist devices. *J Heart Lung Transplant* 2015;34:82-8.
12. Morales DLS, Rossano JW, VanderPluym C, et al. Third annual pediatric interagency registry for mechanical circulatory support (PediMACS) report: preimplant characteristics and outcomes. *Ann Thorac Surg* 2019;107:993-1004.
13. Adachi I, Burki S, Fraser CD Jr. Current status of pediatric ventricular assist device support. *Semin Thorac Cardiovasc*

- Surg Pediatr Card Surg Annu 2017;20:2-8.
14. Peng DM, Koehl DA, Cantor RS, et al. Outcomes of children with congenital heart disease implanted with ventricular assist devices: an analysis of the pediatric interagency registry for mechanical circulatory support (Pedimacs). *J Heart Lung Transplant* 2019;38:420-30.
 15. de By TMMH, Antonides CFJ, Schweiger M, et al. The European registry for patients with mechanical circulatory support (EUROMACS): second EUROMACS paediatric (Paedi-EUROMACS) report. *Eur J Cardiothorac Surg* 2020;57:1038-50.
 16. O'Connor MJ, Lorts A, Davies RR, et al. Early experience with the HeartMate 3 continuous-flow ventricular assist device in pediatric patients and patients with congenital heart disease: a multicenter registry analysis. *J Heart Lung Transplant* 2020;39:573-9.
 17. Conway J, Al-Aklabi M, Granoski D, et al. Supporting pediatric patients with short-term continuous-flow devices. *J Heart Lung Transplant* 2016;35:603-9.
 18. Lorts A, Eghtesady P, Mehegan M, et al. Outcomes of children supported with devices labeled as "temporary" or short term: a report from the pediatric interagency registry for mechanical circulatory support. *J Heart Lung Transplant* 2018;37:54-60.
 19. ClinicalTrials.gov. Pumps for kids, infants and neonates. Available online: <https://clinicaltrials.gov/ct2/show/NCT02954497>. Accessed December 2, 2020.
 20. Pumpkin Trial. Study design. Available online: <http://pumpkintrial.com/Study-Design>. Accessed December 2, 2020.
 21. Mehra MR, Naka Y, Uriel N, et al. A fully magnetically levitated circulatory pump for advanced heart failure. *N Engl J Med* 2017 Feb 2;376:440-50.
 22. Cai AW, Islam S, Hankins SR, Fischer W, Eisen HJ. Mechanical circulatory support in the treatment of advanced heart failure. *Am J Transplant* 2017;17:3020-32.
 23. Giridharan GA, Lee TJ, Ising M, et al. Minutization of mechanical circulatory support systems. *Artif Organs* 2012;36:731-9.
 24. Blume ED, Rosenthal DN, Rossano JW, et al. Outcomes of children implanted with ventricular assist devices in the United States: first analysis of the pediatric interagency registry for mechanical circulatory support (PediMACS). *J Heart Lung Transplant* 2016;35:578-84.
 25. Colombo PC, Mehra MR, Goldstein DJ, et al. Comprehensive analysis of stroke in the long-term cohort of the MOMENTUM 3 study. *Circulation* 2019;139:155-68.
 26. Schweiger M, Lorts A, Conway J. Mechanical circulatory support challenges in pediatric and (adult) congenital heart disease. *Curr Opin Organ Transplant* 2018;23:301-7.
 27. Hollander SA, Chen S, Murray JM, et al. Rehospitalization patterns in pediatric outpatients with continuous-flow VADs. *ASAIO J* 2017;63:476-81.
 28. VanderPluym CJ, Adachi I, Niebler R, et al. Outcomes of children supported with an intracorporeal continuous-flow left ventricular assist system. *J Heart Lung Transplant* 2019;38:385-93.
 29. Sert DE, Kocabeyoglu SS, Kervan U, et al. Cerebrovascular events in children on intracorporeal continuous-flow left ventricular assist devices. *Artif Organs* 2020;44:1251-8.
 30. Pac M, Kocabeyoglu SS, Kervan U, et al. Third generation ventricular assist device: mid-term outcomes of the HeartWare HVAD in pediatric patients. *Artif Organs* 2018;42:141-7.
 31. Simpson KE, Kirklin JK, Cantor RS, et al. Right heart failure with left ventricular assist device implantation in children: an analysis of the Pedimacs registry database. *J Heart Lung Transplant* 2020;39:231-40.

Cite this article as: Lichtenstein KM, Tunuguntla HP, Peng DM, Buchholz H, Conway J. Pediatric ventricular assist device registries: update and perspectives in the era of miniaturized continuous-flow pumps. *Ann Cardiothorac Surg* 2021;10(3):329-338. doi: 10.21037/acs-2020-cfmcs-18