Review Article

The importance of mechanical circulatory support on pediatric waitlist and post heart transplant survival: a narrative review

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Background and Objective: While heart transplantation for children with end-stage heart failure has been available for more than 50 years, outcomes on the waitlist and as well as post-transplant outcomes have not always been favorable. Post-transplant survival initially showed marked improvement with better and better immunosuppression regimens. However, waitlist outcomes (as well as those deemed too sick to list) remained unfortunately low. With the introduction of mechanical circulatory support (MCS) in the 1970s, a new hope for the those with end-stage heart failure emerged. This paper will review the past, present and what is on the horizon for MCS as a bridge to heart transplantation in pediatric patients.

Methods: A search of peer-reviewed scientific studies published in English from 1990–2020 using the PubMed database with keywords including extracorporeal membrane oxygenation (ECMO), ventricular assist devices (VAD) and heart transplantation all focusing on pediatrics.

Key Content and Findings: Initially ECMO and intra-aortic balloon pumps were tried but both waitlist and post-transplant mortality were unacceptable. Paracorporeal pulsatile VAD ushered in better waitlist survival and intracorporeal continuous-flow VAD borrowed from the adults have increased safety both before and after transplant. Over the last couple of decades that hope of MCS has turned into remarkable advances in pre- and post-transplant outcomes.

Conclusions: As survival continues to improve, there is now a push to decrease morbidity seen in many of the early devices. Even the current devices available continue to exhibit unreasonably high complication rates, especially in the smaller and more complex patients.

Keywords: Pediatrics; mechanical circulatory support (MCS); ventricular assist device (VAD); heart transplantation

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Introduction

Since the first adult heart transplant (1) and pediatric heart transplant (2) both in 1967, the need for pre-operative management of end-stage heart failure has been apparent. The first decade saw patients transplanted only from geographical and temporal luck—the patient was in need and stable enough, while the donor organ became available nearby. However, this strategy significantly limited recipients' ability to get a donor heart. Therefore, ways to bridge patients with end-stage heart failure for longer periods of time were necessary and have continued to evolve. This narrative review will cover the history and the current options for mechanical circulatory support (MCS) as a bridge to transplant, as well as the impact on

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Table 1 The search strategy summary

Items	Specification
Date of search	January 20th, 2021
Databases and other sources searched	PubMed
Search terms used	Pediatric, mechanical circulatory support (MCS), extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), heart transplantation
Timeframe	1990–2020
Inclusion and exclusion criteria	Inclusion criteria: all studies including case reports, case series, cohort studies, registry reports and prospective trials; exclusion criteria: non-English studies
Selection process	Citation selection was performed by the author

post-transplant survival. The following article is presented in accordance with the Narrative Review reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-21-10/rc).

Methods

A search of peer-reviewed scientific studies published in English from 1990–2020 was performed using the PubMed database (see details in *Table 1*). Keywords included pediatric MCS, pediatric extracorporeal membrane oxygenation (ECMO), pediatric ventricular assist devices (VAD), and pediatric heart transplantation. Reference lists of selected papers were also reviewed to identify relevant studies pertaining to this subject. Relevant articles including case reports, case series, cohort studies, registry reports, and prospective trials were included in this narrative review.

Historical background

ECMO

ECMO, or historically referred to as veno-arterial cardiopulmonary bypass, was first used as a bridge to transplant in early 1980s (3). It became the initial standard of care for infants and children in need of mechanical support as a bridge to transplant. However, reviews continue to show poor outcomes as a bridge to transplant both on the waitlist and post-transplant (4,5).

Intra-aortic balloon pumps

Following some of the success in the adult MCS world, attempts at using intra-aortic balloon pumps as a means of MCS were also employed in the 1980s and 1990s (6,7). However, overall success was limited because of difficulty in placing in small vessels, in synchronizing the device with the faster pediatric heart rates, and in providing sufficient cardiac output support.

The first VAD

The VAD implanted in a pediatric patient was an adult device called the DeBakey VAD (MicroMed Technology, Houston, TX, USA) in a 6-year-old in 1967, although the indication was for cardiac recovery (8). Attempts to use adult-sized devices, both pulsatile and non-pulsatile, continued throughout the 1970s and into the 1980s (9). The next big step forward was in 1989, this time in Germany, where an adult-sized (50 mL) Berlin Heart EXCOR (Berlin Heart GmbH, Berlin, Germany) was implanted in an 8-year-old who survived to transplant (10). In the 1990s, the concept of pediatric-specific devices started to develop with trials in Japan (11), Germany (10), Australia (12) and the United States (13). Thoratec VAD (Thoratec Corp, Pleasanton, CA, USA), another adult-designed device, was one of the first more widely used in pediatrics in the United States, although due to the size it was limited to larger adolescent patients. Early experience showed modest results with significant thromboembolic complications (14). *Table 2* shows many of the VADs that are used in the pediatric population.

Berlin Heart: the game changer

In Germany in 1991, Berlin Heart used the EXCOR design of a pneumatic, pulsatile, paracorporeal pump into smaller pediatric-appropriate sizes. Other devices were designed and tested around that time (15), but were largely abandoned

Table 2 Available ventricular assist devices

Device	Type	FDA/CE mark approval in adults (year)	FDA/CE mark approval in pediatrics (year)
Berlin Heart EXCOR	Paracorporeal pulsatile flow	No/yes (N/A, 1996)	Yes, all ages (2011/1996)
HeartWare HVAD	Intracorporeal continuous flow	Yes (2012/2009)	No
HeartMate 3	Intracorporeal continuous flow	Yes (2017/2015)	Yes (2020/2015)
SynCardia Total Artificial Heart	Intracorporeal pulsatile flow	Yes (2004/1999)	Yes, if adequate size (2020/1999)
Jarvik 2015	Intracorporeal continuous flow	No	No
HeartAssist 5	Intracorporeal continuous flow	No	Yes, 5–16 years (BSA 0.7–1.5 m^2) (2004/2001)
Centrimag/Pedimag	Paracorporeal continuous flow	Yes, Centrimag* (2009/2002)	No
Rotaflow	Paracorporeal continuous flow	No	No
Impella	Percutaneous continuous flow	Yes** (2015/2012)	RP only, BSA >1.5 m^{2}** (2018/2014)
TandemHeart	Percutaneous continuous flow	No	No

*, up to 30 days of support; **, up to 4 days for 2.5 and CP sizes, and 14 days for RP, 5.0, LD and 5.5 sizes.

due to the comparative success of the Berlin Heart EXCOR. Hetzer *et al*. report the first European series of patients on the original Berlin Heart, and showed remarkable success for the time (16). The device received European marketing approval in 1996, with Canada (2009) and the United States (2011) following later. The design includes pumps of 10, 15, 25, 30, 50 and 60 mL in size. The growth of its use expanded significantly through the first decade of the 21st century, increasing from 1–4 implants per year in the US from 2000–2004 to more than 80 by the end of the decade (17).

Early experience

European and North American trials showed improved outcomes compared to ECMO for pediatric patients bridged with Berlin Heart as well as post-transplant outcomes approaching those transplanted on inotropic support (18,19). Initial North American data regarding compassionate use in 73 patients showed 70% were able to be bridged to transplant with younger age and biventricular support identified as risk factors for death (20). A single center in Germany showed that of 122 cases, 46% were bridged to transplant while another nearly 15% were explanted after myocardial recovery (21). In the second half of the 2000s, use of the Berlin Heart increased dramatically, and with it, the complexity of cases increased as well. From 2007–2010, 204 devices were implanted in North America, with 2/3 under compassionate use (17). The compassionate use group was smaller, enrolled many more patients with congenital heart disease including 19 with single ventricle physiology [none in the Investigational Device Exemption (IDE) group] and were more likely to be on ECMO prior to cannulation. Not surprisingly, compared with IDE subjects, children implanted under compassionate use were less likely to survive to transplant (53% *vs.* 85%, P<0.01) and were more likely to die (34% *vs.* 7%; P<0.01). Also important from this study was that the stroke rate, a known dreaded complication, remained high at 29%, despite the increasing complexity of the patient population. However, in a separate analysis, those patients who survived to transplant on a Berlin Heart had similar post-transplant 1-year survival to those transplanted as similar priority status patients without VAD (88.7% *vs.* 89.3%, P=0.005) (22).

Current outcomes

In the last decade, both morbidity and mortality continue to decrease. In a multicenter North American trial, 21 patients were supported on Berlin Heart EXCOR with a direct thrombin inhibitor (bivalirudin or argatroban) as the primary anticoagulant, as opposed to heparin, and had 90% survival to transplant (23). Using that knowledge, the Advanced Cardiac Therapies Improving Outcomes Network (ACTION), implemented a quality improvement initiative that dropped the stroke rate on device down to 12% (24). Another major issue for the Berlin Heart has been the increased risk of morbidity and mortality for the smallest

patients. That too, continues to improve with better survival and fewer strokes for patients younger than 1 year or <10 kg, although still not as favorable as older or larger children (25,26). Major challenges still remain, though, as outcomes for patients with single ventricle physiology continue to be overall poor (27). The FDA post-approval surveillance study report published this year shows how far the field has come. Despite significantly more risk factors such as being younger, smaller, and more likely to have congenital heart disease, the post-marketing approval surveillance study group had an 86% 6-month success rate (transplant, explant with recovery or still on device) compared to 76% for previously reported Berlin Heart study group (28). All adverse events improved including stroke (11.5 *vs.* 3.99 events per 100 patient months), major bleeding (33.9 *vs.* 6 events per 100 patient months), and major infection (40.36 *vs.* 10.39 events per 100 patient months). Frequency of pump exchanges also decreased 40%. Similarly, centers across the globe continue to show improvements in waitlist and post-transplant mortality (29-32).

Intracorporeal devices: continuing to borrow from adults

Early experiences

Early reports of intracorporeal continuous-flow device use in near-adult-sized adolescents started the wave of adapting new devices for pediatric use. The DeBakey VAD Child, now called the HeartAssist 5 (ReliantHeart, Inc., Houston TX, USA), a smaller version of the adult-sized DeBakey VAD, is an axial-flow pump that earned European approval in 2001 and US approval in 2004. The first successful use of the device as a bridge to pediatric transplant occurred a year later (33). However, due to its relatively large size and multiple reports of neurologic complications it has not been widely adopted in pediatrics (34). HeartMate II (Abbott Corporation, Abbott Park, IL, USA) is an axial flow device that helped usher in a significant improvement in VAD outcomes in adults. Experience in pediatrics was again limited due to its large size, but still showed important mortality advantages. In one of the first large case series evaluating intracorporeal devices in pediatrics, Cabrera *et al.* showed excellent positive outcomes with 96% either transplanted, alive on device or recovered (35). HeartWare HVAD (Medtronic, Minneapolis, MN, USA), a centrifugal continuous-flow pump, received approval in adults in the US in 2012. The first reported cases of HVAD use in pediatrics were in Europe in the early 2010s (36), with the first reported case in the US coming shortly after (37).

Current outcomes

Success in bridging pediatric patients to heart transplant with the HeartWare HVAD is now a worldwide effort. In a study by Conway *et al.*, the authors showed overall positive results regardless of geographic location (38). Notably, need for temporary right-sided support (HR 10.65, 95% CI: 12.53–44.81, P=0.001) or pump exchange (HR 7.9, 95% CI: 1.8–34.2, P=0.006) were associated with death on device. Data from the Pediatric Interagency Registry for Mechanically Assisted Circulatory Support (Pedimacs) registry showed that overall success with HeartWare as a bridge to transplant was on par with adult outcomes (39). Six-month survival was 86.5% compared to 93% for young adults (19–30 years old), which was not statistically significant. Similar results have been shown in the European Registry for Patients with Mechanical Circulatory Support Paediatric (Paedi-Euromacs) (32). With the improving success of intracorporeal devices as single left ventricular support, pediatric centers continue to push the boundaries of who can be supported. Use of intracorporeal devices for congenital heart disease, including failing single ventricle Fontan physiology, is expanding and improving (40). The earliest reports of using HVAD biventricular support (BiVAD) showed promise with 3 patients successfully bridged to transplant (41). Multicenter outcomes from intracorporeal BiVAD configuration still show success although with clearly added risk compared to LVAD-only (42). One of the newer devices gaining adoption in pediatrics is the HeartMate 3 (Abbott Corporation, Abbott Park, IL), another intracorporeal, centrifugal pump. Advantages to this device have been shown in the adult population including less stroke and less pump thrombosis (43). ACTION put together the combined experience of participating centers and demonstrated the efficacy of the HeartMate 3 in 35 children, including 17% with congenital heart disease (44). There was only one death (97% survival), and 57% were successfully bridged to transplant, while the rest remained alive on device. Importantly, there were no episodes of stroke or pump thrombosis. This work led HeartMate 3 to earn FDA-approval for pediatric patients in 2020.

Post-transplant outcomes after MCS

Early outcomes

Evaluation of post-transplant survival after bridge from

ECMO showed overall poor results. In Toronto, Canada, post-transplant survival using ECMO as a bridge to transplant was only 67% and 52% at 1 and 5 years, respectively (45). A multi-center North American study from 1994–2009 showed even worse post-transplant survival for children bridged with ECMO with only 47% surviving to discharge (4). As VADs became more common as an MCS modality for bridge to transplant, there was early recognition of the potential post-transplant benefits. In a study mentioned earlier reviewing Berlin Heart pediatric patients bridged to transplant, 1-year survival was 87.1% (22). Early review of all VAD types in pediatrics from 1995 to 2011, showed paracorporeal VADs were associated with a higher post-transplant mortality (OR 3.0, 95% CI: 0.8–10.6) while other types were associated with lower post-transplant mortality (OR 0.5, 95% CI: 0.2–1.0) compared to no MCS (46). Evaluation of early continuous-flow devices including both HeartMate II (n=80) and HeartWare (n=58) again showed improvingly favorable post-transplant outcomes with 1-year and 5-year survival of 100% and 88%, respectively (47).

Current outcomes

As the pediatric heart transplant community gained experience, including better anticoagulation strategies and better timing for implantation, overall post-transplant outcomes have continued to improve. In a Pedimacs and Pediatric Heart Transplant Study (PHTS) linkage study, there were no differences in post-transplant outcomes including 1-year survival (96% *vs*. 93%), freedom from infection (81% *vs*. 79%) or freedom from rejection (71% *vs*. 74%) between those bridged with a VAD compared to those bridged without a VAD, despite having greater pre-listing illness severity (48). Most notably, the authors conclude that "VAD as a bridge to transplant mitigates severity of illness in children." Similar post-transplant outcomes were noted in review of pediatric VAD use across the world including in Spain (49), Australia (50) and Turkey (51). Looking specifically at one of the more challenging populations to support, children with congenital heart disease showed similar 1-year (84% *vs*. 87%) and 5-year (72% *vs*. 75%) (P=0.694) post-transplant survival compared to children with congenital heart disease bridged without VAD (52). In the most recent report on pediatric heart transplantation from the International Society for Heart and Lung Transplantation (ISHLT), Kaplan-Meier estimates showed no difference in post-transplant survival between VAD or total artificial heart (TAH) *vs*. no MCS (P=0.982), while there was still a significant difference for ECMO *vs*. VAD or TAH (P=0.0062) and no MCS (P=0.0037) (53).

In regards to the most common devices, Berlin Heart EXCOR has shown similar 30-day, 1-year and 5-year post-transplant survival compared to a similar non-MCS cohort (94%, 90% and 72% *vs*. 98%, 91% and 77%, P=0.16) (54). Even better 5-year results (81% survival) were seen specifically in patients bridged as part of the Berlin Heart IDE trial (55). One-year survival for patients with continuous-flow devices (mostly HeartWare in this study) was 97.3% (48). Even more remarkable, no post-transplant mortality to date has been noted for pediatric patients bridged with the HeartMate 3 device, although overall numbers remain small (44).

Discussion

With waitlist mortality for pediatric patients on VAD continuing to improve and post-transplant survival equal to patients bridged without MCS, the pediatric VAD and transplant community has started to shift focus to other key areas including reducing morbidity and bridge to bridge management.

Stroke was one of the biggest causes of morbidity (and mortality) for early devices. It continues to haunt pediatric practitioners despite improvements in devices, patient selection and management. While single-center studies and small case series have been helpful to introduce novel management strategies and surgical techniques, the small number of patients are insufficient to create evidence-based recommendations. Because individual centers all have relatively few pediatric patients, registries such as Pedimacs and Euromacs have created larger data repositories that have helped further define complications and morbidities with pediatric VAD use including stroke rate, infection, bleeding, and inpatient length of stay. The latest effort to advance the field further and faster is through a learning network that has both elements of data registry and quality improvement. ACTION is leading this charge now with more than 50 sites across the world under the motto "steal shamelessly and share seamlessly" (56). As mentioned earlier, through this network there have been significant inroads in stroke reduction for paracorporeal pumps and regulatory approval for devices in pediatrics. Ongoing work continues to push current devices such as SynCardia Total Artificial Heart (SynCardia Systems Inc., Tucson, AZ, USA) (57) and new devices such as the Jarvik 2015 (Jarvik Inc., New York, NY, USA) (58) to better support children as a bridge to heart transplant.

Bridge to bridge management is the idea that before a patient is deemed stable enough for a durable VAD such as a Berlin Heart, HeartWare or HeartMate 3, that a temporizing form of mechanical support may be necessary and could potentially improve outcomes. VA-ECMO remains the gold-standard for temporizing MCS in pediatric patients with cardiogenic shock in part because of the ease and rapidity of deployment as well as full cardiopulmonary support. Other temporary paracorporeal devices that are implanted surgically include Rotaflow (Maquet, Rastatt, Germany) and Pedimag/Centrimag (Abbott Laboratories, Abbott Park, IL, USA). These devices can be placed with ECMO cannulae, or have been used with Berlin Heart cannulae, thereby simplifying conversion to the EXCOR (59,60). Some centers have used these devices longer-term as a bridge to transplant as well with mixed success, although often in the setting of the sickest patients (61). Finally, more interest has been shown in recent years for percutaneous bridge to bridge options such as the TandemHeart (CardiacAssist, Pittsburgh, PA, USA) or Impella (Abiomed, Danvers, MA, USA) devices, which are via femoral or axillary artery access (62). There is limited adult data of Impella use as direct bridge to transplant in settings where waitlist times are expected to be very short (63). Ultimately, these strategies have come about due to the unacceptably high morbidity and mortality among children presenting with acute cardiogenic shock.

Conclusions

Half a century of advancements has yielded tremendous results in the field of MCS and heart transplantation. Children of all ages, sizes and anatomies are being better supported than ever before with less waitlist mortality despite increased disease severity and excellent post-transplant outcomes. However, that enthusiasm continues to be tempered by the residual morbidity of today's devices. More work is needed to improve patient selection, management of current devices available, design of newer and safer devices, and post-transplant care.

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Footnote

Reporting Checklist: The author has completed the Narrative Review reporting checklist. Available at https://pm.amegroups.com/article/view/10.21037/pm-21-10/rc

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