Mechanical circulatory support in pediatrics

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There is no reliable published data on the overall prevalence or incidence of heart failure (HF) in children. However, the success of mechanical circulatory support (MCS) in management of HF has raised the prospect of a previously unavailable treatment modality. Orthotopic heart transplant (OHTx) remains the gold standard treatment, but the number of patients requiring this treatment far outweighs the donor availability. It is therefore not surprising to see the popularity of various MCS modalities, with different devices ranging from veno-arterial extra corporeal membrane oxygenation (VA-ECMO) to ventricular assist devices (VADs), which are either para-corporeal or intra-corporeal, with pulsatile or continuous flow. Indication, timing and the choice of the type of mechanical support are crucial so in order to avoid potential lethal complications such as hemorrhage, thrombo-embolism and infections. In the pediatric population, MCS is used mainly as bridge to transplantation but can be used as bridge to recovery in patients with acute myocarditis or following open-heart surgery. Active research is currently underway to develop newer and more durable devices that will assist the pediatric population across all age groups. This research will support different pathologies that have lower incidences of major morbidities, particularly as greater durations of MCS are expected due to a paucity of donors for OHTx. The combined experience developed through the usage of different devices in pediatric and adult populations has led to the to the application of MCS in some subgroups of grown–up congenital heart diseases (CHDs) patients, particularly those with systemic right ventricular failure.

Keywords: Pediatric heart failure; extra corporeal membrane oxygenator (ECMO); heart transplantation; congenital; ventricular assist devices (VADs); mechanical circulatory support (MCS)

Introduction

The etiology of end-stage heart failure (HF) differs between the pediatric and adult populations; the former being mainly affected by cardiomyopathies (CMPs) that are either surgically treated or untreated congenital heart diseases (CHDs), and the latter mainly affected by ischemic myocardial damage due to coronary artery disease and primary or secondary CMPs (1).

The number of admissions for pediatric patients in HF has increased over 30% in recent years (2,3), primarily because of better treatment modalities, longer survival of surgically treated patients with CHDs and a better understanding and early recognition of CMPs.

Hsu and Pearson have conducted a meta-analysis of different studies concluding that 12,000 to 35,000 children have HF caused by either CHDs or CMPs in the United States (4). This would indicate a prevalence of 164-480 per million children. Rosenthal *et al.* matched the HF in the pediatric and adult cohorts in a cross-sectional study using two large inpatient datasets. Of the 5,610 children with HF, 57% were infants (less than one-year age) with HF as their primary or secondary diagnosis (5). A striking difference was observed in the numbers of children having CHDs or cardiac surgery as a causative or contributing factor for HF, compared to the adult population (61% *vs.* 1%). CHDs was much also more common (82%) in the infant with HF.

The preferred treatment for end-stage HF refractory to medical management is a short- or mid-term mechanical circulatory support (MCS), using a system like veno-

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arterial extracorporeal membrane oxygenation (VA-ECMO) with a centrifugal pump, or long term MCS such as ventricular-assist devices (VADs) as bridge to orthotopic heart transplant (OHTx). While heart transplantation remains the gold standard treatment, the number of suitable pediatric donors and OHTx worldwide has not increased for more than a decade, ranging between only 400-450 cases per year (3). Therefore, the development of an alternative treatment is warranted, and pediatric VADs are now gaining increasing attention. Ultimately, the number of pediatric patients will never be enough for the manufactures to justify the expenses for a limited market, reducing the range of available choices.

Devices for pediatric MCS

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO)

VA-ECMO is the most commonly used system, with the Extracorporeal Life Support Organization reporting over 3,500 cases in US patients (6). The advantages of VA-ECMO include its flexibility as it can be deployed with central or peripheral cannulation. Furthermore, it is easily deployed in the acute setting and is thus useful in supporting children with associated respiratory and renal failure. However, VA-ECMO is a relatively short-term device; it can be invasive and complex, requiring high intensive care management, preventing mobilization and effective physical rehabilitation during support. Due to long tubing, the oxygenator, and other tools connected to the circuit (e.g., CVVH, filters), it triggers an intense inflammatory response. It is also associated with serious complications such as embolic events, hemorrhage, organ damage and particularly neurological insults. As afterload increases with VA-ECMO flow, the need for left ventricle (LV) decompression via either atrial septostomy or through left heart venting is sometimes required.

Because of the presence of an oxygenator, VA-ECMO remains the only option of support when significant hypoxemia and respiratory failure contribute to the underlying pathophysiology (7). More importantly, VA-ECMO is a resuscitation tool that provides support for decision-making (8). If heart function promptly recovers, the child should be weaned from VA-ECMO, otherwise circulation can be transitioned to a long-term support device (9). For that reason, in case of central approach, implantation of Berlin Heart Excor (BHE) cannulae type

for VA-ECMO can be considered by surgeons to facilitate switching from VA-ECMO to a longer-term cardiac support system.

Short-term VADs

Historically, centrifugal pump-based systems have been the most common form of VADs support in children. Currently the devices available are: Bio-Medicus BP-50 (Medtronic; Minneapolis, MN, USA), CentriMag (Levitronix LLC; Waltham, MA, UK), Jostra RotaFlow Centrifugal Pump (MAQUET Cardiovascular; Wayne, NJ, USA), and TandemHeart (CardiacAssist, Inc.; Pittsburgh, PA, USA). These systems employ a constrained vortex, producing a non-pulsatile flow, and are both preload and afterload dependent. Short-term devices are usually employed for acute pathologies such as myocarditis, post-cardiotomy ventricular dysfunction, or acute cardiac graft rejection, with the intention to recover cardiac contractility and allow subsequent VADs explantation ("bridge to recovery"). There is also an emerging use of short-term devices for a "bridge to decision". This strategy is used when a patient's medical history is complicated, where there are extra-cardiac pathologies that are not clearly defined and factors such as genetic or chromosomal abnormalities, or end-organ issues such as neurological sequelae that could make the cardiac transplantation an unviable option. These patients can be converted to a long-term VADs once doubts are resolved and if they are indeed determined to be suitable candidates for recovery or transplant. This has been coined a "bridge-to-bridge" strategy. It is likely with new generation VADs that this kind of support will become less common.

Long-term VADs

VADs provide longer-term support for the failing myocardium and fall into two major categories: para-corporeal and intra-corporeal devices. Para-corporeal devices currently available and used in children include the Thoratec VADs system (Thoratec Laboratories Corp.; Pleasanton, CA, USA), Abiomed BVS5000 and Abiomed AB5000 (Abiomed, Inc.; Danvers, MA, USA), BHE (Berlin Heart AG; Berlin, Germany), and MEDOS HIA VADs (MEDOS Medizintechnik AG; Stolberg, Germany). Intra-corporeal or implantable devices include: the Heartware (Heartware Inc.; Framingham, MA, USA), the MicroMed DeBakey VADs (MicroMed Technologies, Inc.; Houston, TX, USA), the Jarvik 2000 FlowMaker (Jarvik Heart, Inc.; New York, NY,

USA), the Berlin Heart INCOR (Berlin Heart AG; Berlin, Germany), and the Thoratec HeartMate II VADs (Thoratec Laboratories Corp.; Pleasanton, CA, USA).

The only labeled VAD available for neonates and infants is the BHE. BHE facilitates support of both the left and right ventricle. Furthermore, the availability of different sizes of cannulae and pumps allows it to be used in all children regardless of their size and weight (10-12). BHE is a second-generation device and neurological complications vary between 25% and 30% (11,13). Third-generation devices have showed an improved outcome from a cerebrovascular accident point of view, as reported by Kirklin *et al.* (14). Therefore, there is an increasing tendency to use these third generation devices in the pediatric population. It has to be recognized that these devices have not been designed for lower cardiac output and that their use is clearly "off label".

Long-term VADs, either para-corporeal or intra-corporeal, allow for extubation, physical rehabilitation in the hospital setting, and for some devices, the potential for home discharge and outpatient support. Although long-term support for non-transplant candidates whose cardiac MCS function is unlikely to recover is becoming more common in the adult population, this "bridge-to-destination" strategy is currently not an option with a pediatric-specific VAD. Thus currently, long-term para-corporeal VADs in children are mainly used as a "bridge to transplantation".

Perspectives

As a general overview, VA-ECMO should be considered in the acute setting, after cardiac surgery, for impaired cardiac function or when respiratory function is compromised. If recovery is not promptly achieved, a conversion to VADs support is strongly recommended in order to avoid the complications of VA-ECMO circulation. Davies *et al.* (15) demonstrated that the negative effects of VA-ECMO are seen even after patients are successfully bridged to cardiac transplantation. Although more recent papers differ in their findings, this study found a higher rate of post-transplant mortality in patients supported with VA-ECMO compared to those who had VADs support irrespective of diagnosis. Aside from children with CMPs who suffer from a primary alteration of the myocardium, the other growing pediatric population is children with corrected or palliated CHDs, with either univentricular or biventricular circulation. Timing of device implantation is often very important. However, classic guidelines for VAD implantation and

risk factors summation scores have not always successfully applied to children.

A large study of 102 pediatric patients in end-stage HF with end-organ dysfunction requiring multiple inotropes, enrolled in the two licensed centers in UK for implantation of a BHE, shows interesting results. Even if the acuity of these presentations did not change significantly with time as most children were referred to the transplant units for consideration of MCS from their regional cardiology centers, 84% survived to transplant or explant, reflecting the concentration in MCS expertise. However, 25% of patients experienced neurological complications despite aggressive hematological surveillance. In contrast, the stroke risk with the third- and fourth-generation adult centrifugal pumps is much lower, at 10% (16). Surprisingly, multiple factors that were previously identified as predictors of mortality including infancy, use of VA-ECMO pre-VADs implantation, cardiac arrest pre-VADs, bi-ventricular assist device (BiVAD) support and CHD etiology, were not found to be significant (9,17). The only independent risk factors for death were stroke and ongoing ventilation whilst on BHE support. The chance of a successful outcome was highest in dilatative CMP and lowest in MCS in single ventricle patients.

The BHE was first implanted in North America in June 2000, and since then has seen a rapid increase in usage. BHE applied for an investigational device exemption (IDE) trial (18), which started in 2007. The purpose of the study was to determine if the use of the BHE for bridge-to-transplantation in pediatric patients is associated with reasonable assurance of safety. No other pediatric VADs were directly comparable so the FDA agreed that pediatric ECMO patients formed the control group. This prospective, non-randomized, multi-center study enrolled 48 subjects in 17 North American centers, aged from 0 to 16 years. Two groups were created: 24 subjects with body surface area (BSA) <0.7 m^2 (Cohort 1) and 24 subjects with a BSA ≥0.7 m^2 to <1.5 m^2 (Cohort 2). Later, a third cohort was enrolled under Compassionate Use regulation (Cohort 3).

For long-term assistance, we currently use BHE as LVAD or BiVAD and Heartware HVADs at our institution. For both types of devices, we use the same anti-coagulation protocol, which has changed multiple times since our first implant in accordance with our results and experience from other centers. Patients assisted with VADs are not anticoagulated for 24-48 hours to reduce excessive bleeding. Intravenous heparin infusion is then started at 25 units/kg/h and continued during the time of MCS, keeping the anti-Xa

levels between 0.35 and 0.7 units/mL. Once postoperative bleeding ceases, anti-platelet therapy is commenced, starting 1 mg/kg of dipyridamole 6-hourly and thereafter adding aspirin 1 mg/kg twice a day. A value of 7 g/L of hemoglobin is considered the threshold for institution of blood transfusion.

Infection prophylaxis is continued for 48 hours after the implantation using broad-spectrum antibiotics and antifungal drugs. Wound care consists of daily dressings using sterile saline 0.9% and avoiding alcoholic solutions. Once the drains are removed, the wound and cannula dressings are changed twice a week and swabs of the wound and of the cannula sites are sent once a week. After implantation of MCS, all patients are listed urgently for OHTx. However, an institutional protocol has been established in order to allow recovery from VADs. Patients on VADs are undergoing weekly echocardiography and stress test if signs of recovery are found.

Although the use of BHE is well established in CMPs, much less is known regarding its application to children with CHDs, with few studies reported in literature (19-21). Some studies report a higher morbidity and mortality associated with the use of BHE in the CHDs group (22,23). However, in a recent paper from the United States by Almond and colleagues (21), there was no increased risk in CHD patients that received a BHE. Furthermore, the use of VA-ECMO prior to insertion of the BHE was also not a risk factor in the entire cohort. We also found similar results in our overall experience with pediatric MCS (20).

The use of MCS in single ventricle support still remains a challenge. This is due to the complex anatomy, combined with the complex pathophysiology of single ventricle circulation. Indeed, there are only a few papers that discuss this subject (24-26). In our recent report (27), we found that children with CHDs supported with mechanical assist devices for acute or end-stage HF can be satisfactorily bridged to OHTx despite the significant cumulative morbidity. Nearly two-thirds of them survived to discharge after OHTx. Most importantly, single-ventricle compared to the biventricular circulation does not increase the risk for death before OHTx.

Another interesting concept is that patients with end-stage heart disease and severe pulmonary hypertension may become candidates for OHTx after a more or less prolonged duration of BIVAD support (11,28,29). The theoretic basis for VADs implantation in similar cases is that continuous unloading of the LV, provided by the LVAD, lessens left atrial pressure while the antegrade blood flow driven by the right VADs concurrently promotes the decline of pulmonary vascular resistance.

Patients with grown-up congenital heart disease (GUCH) presenting with end-stage HF are normally treated as higher risk patients with a higher risk for OHTx (30), but they are also placed on the waiting list if standard criteria are met. Due to their specific anatomy, these patients require specific transplantation management in regards to the explantation of their donor organs (long aortic arch segment/pulmonary bifurcation up to the hilar region included) and the technical aspects of the implantation phase. Some of them require complex anatomical reconstruction to create a biventricular circulation, such as patients with hypoplastic left heart syndrome, tricuspid atresia, any type of univentricular heart after cavo-pulmonary shunt or Fontan completion, or dextrocardia. If GUCH patients are not eligible for OHTx or suffer from severe worsening of clinical symptoms while on the waiting list, a MCS should be implanted (31) either as destination therapy or as bridge to transplant. Particular cases are those patients requiring MCS due to HF following an atrial switch operation (Senning or Mustard procedure) (32-34).

From 1998 to March 2014, our institution performed a total of 127 MCS episodes as bridge to OHTx. The leading cause of MCS requirement was CMPs in two-thirds of these patients. A total of 87 Excor Berlin Heart devices were implanted as well as five Heartware and seven Medos devices. VA-ECMO was performed in 23 cases and Levitronix devices implanted in six. Twenty-nine patients had end-stage HF following correction or palliation for CHDs: 15 with biventricular and 14 with univentricular physiology.

In the univentricular group, seven patients were assisted with VA-ECMO (four after Fontan completion, two after cavo-pulmonary shunt and one after Norwood stage I), and seven patients with Excor Berlin Heart (five after cavo-pulmonary shunt, one after Norwood stage I and one after Damus-Kaye-Stansel anastomosis and modified Blalock-Taussig shunt). The overall survival to OHTx or explant in all CHDs patients was 72%, and survival to discharge was 59%, with no statistical difference between those with univentricular or biventricular circulation (27).

A recent review on the experience of BHE in children in the US, focusing on patients with a single functional ventricle (35), supports our data in suggesting that only a maximum of several weeks of support before OHTx is needed for a successful outcome. Notably however, this study experienced a lower survival to OHTx or recovery (42.3%) in the single ventricle group compared to the

biventricular group (72.5%).

An interesting perspective for the future will be the treatment of patients with severe HF due to primary muscular dystrophies such as Duchenne disease, and adolescents with neurological impairment that prevent their enrollment in standard transplant lists. In these particular cases, a VADs implant should be advocated (36).

For the future, we are awaiting new devices to be tested and made available for clinical trials. In the United States, the National Heart, Lung, and Blood Institute (NHLBI) launched the four-year Pediatric Circulatory Support Program in 2011 (following a previous trial started in 2004) called Pumps for Kids, Infants, and Neonates (PumpKIN) Trial (37), including five different devices: the pediatric cardiopulmonary assist system (pCAS, Ension, Inc.; Pittsburgh, PA, USA), child Jarvik 2000 (Jarvik Heart, Inc.; New York, NY, USA), PediaFlow (University of Pittsburgh), and PediPL system (Levitronix and University of Maryland). Clinical studies are needed to satisfy the requirements for approval of Humanitarian Device Exemptions, so that these devices can be suitably marketed in the United States. The clinical evidence collected in the PumpKIN IDE clinical trial will be submitted to the FDA in the Humanitarian Device Exemption applications for the pediatric circulatory support devices in the study. The intention is that the devices in the program will provide adequate circulatory support for newborns, infants, and children weighing under 55 pounds who have HF due to CHDs or acquired heart disease. Among other specifications these devices are intended to support these children for one to six months, be sufficiently small and reasonably portable, and be able to be routinely positioned and functioning in less than one hour (38). Future devices, together with regenerative therapy involving stem cells, are likely to improve the outcomes of children with severe HF.

Acknowledgements

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