Seminars in Pediatric Surgery 30 (2021) 151039

Contents lists available at ScienceDirect

Seminars in Pediatric Surgery

journal homepage: www.elsevier.com/locate/sempedsurg

Pediatric heart transplant

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ARTICLE INFO

Keywords:
Pediatric transplant
Heart transplant
Outcomes
Single ventricle
Ventricular assist device
Congenital Heart
Fontan

ABSTRACT

Pediatric heart transplantation has additional and unique aspects from standard pediatric heart surgery and adult heart transplantation. The purpose of this article is to review pediatric heart transplantation and special surgical considerations. The methods used by the authors involved reviewing the literature and surgical techniques surrounding this patient population and procedure. The article presents a general review of the topic including the history, current state, surgical approaches, post-operative management, and outcomes in this patient population.

History

Research on the concept and feasibility of heart transplant became a focus in the 1960's at Stanford University.[1] The importance of controlling the immune system was understood, as well as the counter risk of infection. The first pediatric cardiac transplant was performed in an infant December 6, 1967 by Dr Adrian Kantrowitz, three days after the first heart transplant in an adult.[1,2] Unfortunately, the child died 612 hours post operatively. It was recognized that to have long term success, there needed to be a medicine for effective immunosuppression. With the emergence of Cyclosporin in the 1970s, a new era began. It was previously thought that the first successful pediatric transplant, subsequent to the original, was in 1984, but a recent study discovered there were 30 children transplanted before 1982 whose data were captured retrospectively due to being performed before databases were established.[3] The cohort entered consisted of children with both cardiomyopathy (CM) (n=18) and congenital heart disease (CHD) (n=5) .[3] There were five patients that the cause was not reported.[3] The median patient survival was 3.5 years; however, the graft survival was 0.6 years with a 1-year conditional graft survival of 4.6 years.[3]

Current landscape

The International Society of Heart and Lung Transplant (ISHLT) Thoracic Registry was created in 1983 to capture multicenter pediatric and adult transplant data with data collection throughout the life of the transplant patient/graft. The registry collects a multitude of information (details of the data components are available on the registry website https://ishlt.org/registries/ttx-registry). Using the data set, there are extensive analyses which result in slide sets publicly available for review at https://ishltregistries.org/registries/slides.asp. The "Heart Pediatrics" slide set from 2019 will be used to look at the current landscape with e-slide numbers referring to the exact slide for reference.[4]

The latest data from 2017 shows that there are 117 centers that perform pediatric heart transplants, 56 of which are in the United States (eSlide 4). Among the centers the frequency of heart transplants per year vary with a lot of centers being small programs that do <4 transplants a year. There are 154 centers that average 1–4 transplants a year, 35 centers that average 5–9 transplants a year and 21 centers that average more than 10 transplants a year (eSlide 5). Between 2010 and 2018, 210 pediatric cardiac transplants were performed with 45.5% being done at centers who average >10 transplants a year (eSlide 5).

Recipient data

Recipient characteristics include an age distribution that is bimodal with most transplants (n= 1800) being done in children <1 year of age, followed by children 14 to 17 years old (n=>400 per year) (eSlide9). Looking at the most recent era, 2010–2018, 57% of children <1-year-old were transplanted secondary to CHD (eSlide 16). CM was the leading cause in all other age groups (eSlide 17–19).

Different levels of mechanical support are used prior to transplant and effect overall survival. With the development and use of ventricular assist devices (VAD), there has been a shift away from extracorporeal membrane oxygenation (ECMO) as the main form of mechanical circulatory support (eSlide 21–22). Although VADs are

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https://doi.org/10.1016/j.sempedsurg.2021.151039
1055-8586/

now being used in patients with CHD, a majority of transplant recipients have a VAD secondary to dilated cardiomyopathy (DCM) (53%) versus CHD (14.3%) (eSlide 23).

Sensitization is the creation of antibodies to foreign proteins exposed to recipient's blood stream. This is another important factor that can affect heart transplant outcomes and is tracked by the registry. During the evaluation process, a recipient's blood is tested for panel reactive antibodies (PRAs) to determine if there are strong antibodies to any proteins, leading to the inability to take specific donors as rejection would be immediate. The result is expressed in a calculated percentage of the population that cannot be a donor for the patient. PRAs >10% is considered sensitized. There has been a gradual increase, shown in the registry data, of patients with significant panel reactive antibodies over time (eSlide26). Children born with CHD have higher PRAs (10.8% had PRA 40–79%; 9.2% had PRA >80%) than patients with DCM (8.5% had PRA 40–79%; 1.9% had >80%)(eSlide 28). This is believed to be due to blood products from previous surgeries, VADs and exposure to homograft material.

Listing to transplant

The data shows us the current landscape and how it has changed over time. What has not changed is that a recipient's clinical status, age, size, blood type, CHD versus CM, and comorbidities are important to take into consideration for length of time on the waitlist, listing status, donor selection and operative planning.

The pediatric heart transplant waitlist mortality was close to 25%, but with the development and incorporation of ventricular assist devices, a publication from 2009 had the overall USA waitlist mortality at 17%.[5] Two studies investigated this further, and both showed similar predictors of mortality on the waitlist: ECMO, ventilatory support, CHD, non-white ethnicity, weight <3 kg, highest listing status and dialysis support.[6] One of the most difficult groups are infants less than 12 months of age with a present waitlist mortality of 25%.[6]

There was a clear need for more organ options for this young population, as their size also made using VADs difficult if not impossible. In 2001, a study by West et al was published in the New England Journal of Medicine demonstrating a medical breakthrough proving ABO blood group incompatible (ABOi) transplants were possible in the young.[7] Blood analysis on infants proved that if an infant had not yet developed significant antibodies against other blood groups, an ABOi transplant could successfully be performed.[7] This strategy has gained wide acceptance, increasing in frequency from <10 patients a year in 2004 to 39–49 transplants a year more recently which reflects 24–40% of transplanted children.[8] Long term studies have been done that prove that these patients have comparable survival rates to ABO compatible recipients in the first year.[8]

Listing status for pediatric patients underwent a change on July 7, 2016 to try to improve the allocation, with the goal of more urgent cases transplanted first. Although it increased representation of some of the pediatric cardiac patient populations, there are still inconsistencies and ongoing discussions of the listing status criteria.

Once on the list, wait times vary as centers screen for an acceptable heart. During that time, donor hearts may be offered that have clear contraindications, but there are those marginal donor offers that are more complex. With pediatric donors being scarce, the community wants to lower the discard rate. An ISHLT consensus statement published in April of 2020, looked at pediatric donor discard rates (star). For the study discard rate was defined as the organ being offered but not accepted by any center(star). Using a survey sent to organ procurement organizations (OPO), the discard rate ranged from 18% to 57%.[9] Trying to look at the exact reasons were difficult, but a United Network of Organ Sharing (UNOS) database study listed the reasons as donor age, non-O blood type, Centers for Disease Control high risk donor status, left ventricular ejection fraction (LVEF) <50%, or inotropic support.[10] A study by Godown et al. distributed a survey to transplant centers looking at donor acceptance practice variation.[11] They received responses from 130 centers from 17 countries that demonstrated a wide range of acceptance parameters including: optimum donor to recipient weight ratio with the lower limit varying from 50% to 150% and an upper range of 120%-350%; maximum donor age of 25–75 years old; and minimum acceptable LVEF 30–60%.[11] There are many studies being published with outcomes from taking "marginal donors" trying to improve donor utilization, hopefully leading to lower waitlist mortality.

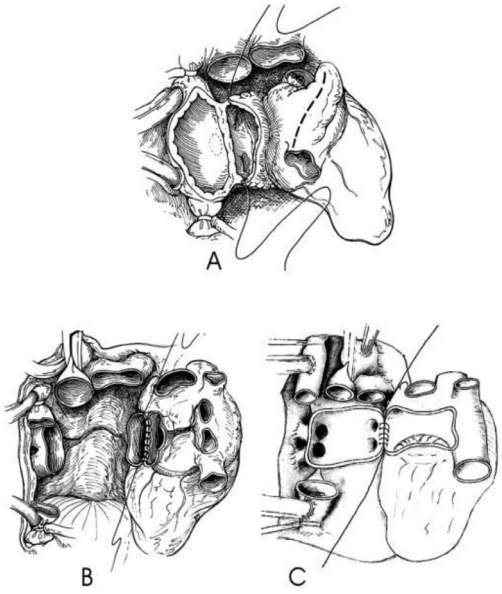

Fig. 1. Schematic drawing of the standard biatrial technique (A) total heterotopic technique (B) and bicaval technique (C). (Reprinted from The Journal of Thoracic and Cardiovascular Surgery, 134 (5), Schnoor M, Schäfer T, Lühmann D, Sievers H, Bicaval versus standard technique in orthotopic heart transplantation: A systematic review and meta-analysis, 1322–1331. 2007, with permission from Elsevier.).

Heart transplant techniques

There are three described techniques for heart transplant (See Fig. 1). The bi-atrial technique was first described in the 1960s and was widely used into the 1990s. It entails anastomosing the donor to recipient left atrium (LA), right atrium (RA), aorta (Ao) and pulmonary artery (PA). It is technically relatively simple and reproducible, but concerns eventually arose regarding atrial dysfunction, conduction disturbances and atrioventricular valve dysfunction. The bi-caval technique which was introduced in the 1990s preserves the donor RA and is widely used today. It requires anastomosing the donor to recipient LA, inferior vena cava (IVC), superior vena cava (SVC), PA and Ao.[12] While it is also reproducible and alleviates many concerns from the bi-atrial technique, it does introduce two sites (SVC and IVC) of potential anastomotic stricture that may be exaggerated in small pediatric patients.[13] The third technique, called total heterotopic cardiac transplantation, was first described in the late 1980s. It is similar to the bi-caval technique but also preserves the donor LA by anastomosing the right and left pulmonary veins separately and preserving a bridge of tissue between them. It is technically more challenging and time consuming; therefore, it is not as widely uti-

lized as the previous two techniques. A comprehensive UNOS review of 20,999 heart transplants done between 1997 and 2007, noted the use of the bi-atrial technique fell from 97.6% to 34.7%. During the same time period, the bi-caval technique use rose from 0.2% to 62.0%. This same review found a lower frequency of permanent pacemaker requirement and a survival advantage of the bi-caval technique over the bi-atrial technique. It is recommended when technically feasible, the bi-caval technique should be utilized.[12]

Impact of VAD

Some pediatric heart failure patients present for heart transplant having never undergone prior heart surgery and the transplant can be performed with one of the above described techniques in a field free of adhesions. Many of these patients, however, are supported with VADs to augment cardiac output and improve end organ function in the time leading up to receiving an organ. While there are numerous devices and configurations, they all consist of a pump inflow cannula, typically sewn to the left ventricle, and a pump outflow cannula, typically sewn to the ascending aorta. Depending on patient size and specific assist device, the actual pump can be intra-corporeal or extra-corporeal. Resection of these devices with recipient cardiectomy at the time of transplant can be tedious and time-consuming. This time must be considered in the transplant process. Nevertheless, the use of pediatric VADs has improved waitlist outcomes and survival to transplant with post-transplant outcomes equivalent to those patients medically supported.[14] Thus, VADs are being utilized on an increasing number of pediatric heart failure patients.

Anatomic variability and single ventricle

In contrast to non-congenital CM, patients with underlying CHD can present additional surgical dilemmas. They can have significant deficiencies in size or number of cardiac chambers. They may also have hypoplastic or absent great arteries arising from the heart. Abnormalities in systemic and pulmonary veins, related or unrelated to abdominal situs, are common in these patients. A vast majority of patients born with CHD have palliative or corrective procedures as the first line of treatment. Therefore, when these patients fail and present for cardiac transplant, it is almost uniformly after previous operations and/or catheter interventions. These previous procedures may result in substantial scarring or anastomotic strictures. They may have extensive patch material or indwelling stents that need removed or repaired at the time of transplant. Depending on the specific location, this may add significant ischemic time and morbidity to the transplant. Examples of such are an aortic arch needing repaired that would require deep hypothermic circulatory arrest (DHCA) or a PA stent that requires removal and patch pulmonary arterioplasty. Situs inversus or persistent left-sided SVC can pose additional challenges in re-directing venous return from the left side of the mediastinum into the right-sided donor atrium by complex inter-atrial baffles or direct anastomosis.[13]

In order to understand the challenges for transplantation, the following is a brief overview of a typical staged approach for the single ventricle pathway in a baby born with hypoplastic left heart syndrome. Stage 1 consists of a Norwood procedure in the first week of life. This is a complex operation that directs all blood leaving the heart into a reconstructed aortic arch to provide adequate systemic cardiac output. Pulmonary blood flow is provided by a systemic to PA or right ventricle to PA shunt. After which, the patient remains with shunted physiology until the stage 2 bidirectional Glenn procedure at 3–6 months of life. This operation converts the pulmonary blood flow from the previous shunt to the passive flow from the SVC. The stage 3 Fontan operation completes the single ventricle pathway at 2–5 years of age. This procedure directs the IVC blood to the lungs so that all blood leaving the heart goes to the body and then passively returns to the lungs. Although out of scope of this review, this stage can be completed by baffling the IVC blood across the RA or by anastomosing an extra-cardiac graft to re-direct the IVC blood directly to the PA. Single ventricle patients who present for transplant pose unique obstacles at different stages.

Some patients who are born as poor single ventricle candidates, typically secondary to diminished ventricular or valvular function, may be best served with listing for transplant prior to stage 1 Norwood intervention. This requires maintaining ductal patency for lower body perfusion and bilateral PA bands to restrict pulmonary blood flow while waiting for an organ. Ductal patency can be maintained with prostaglandin or a ductal stent. The aortic arch must be reconstructed at the time of transplant which requires a period of DHCA, harvesting of additional donor aortic arch and careful timing to ensure appropriate donor ischemic time. The branch PAs may need repaired at the banding sites as well.[13] Patients who present with heart failure after stage 1 Norwood procedure should not require DHCA for an aortic arch procedure, but may require PA augmentation at the shunt site or modifications to accommodate for deficient atrial tissue. After the bidirectional Glenn, the SVC is often foreshortened as it was already anastomosed to the right PA and a portion of it is typically left on the right PA to prevent PA stenosis after the transplant. This can be accommodated for by harvesting the entire donor SVC and innominate vein. If a left-sided SVC was present (and therefore a left-sided bidirectional Glenn), this will also need to be routed to the RA. This can be accomplished with either donor innominate vein or a synthetic graft.[13]

Failing Fontan patients comprise a majority of transplanted single ventricle patients and are the most challenging for many reasons. Patients who reach the Fontan stage have undergone at least 2 and usually 3 prior sternotomies and have developed significant adhesions making re-entry hazardous. Single ventricle patients have also been exposed to lower oxygen saturations that result in development of aortopulmonary collateral vessels. These collaterals are not only a volume load on the existing heart that contributes to heart failure but also add intra-operative challenges as they shunt blood that has been pumped to the body directly back to the lungs. This results in the need for supraphysiologic cardiopulmonary bypass flow and increased pulmonary venous return that impedes surgical visualization. Collateral vessels may also contribute to significant post-operative hemorrhage as they are disrupted during cardiectomy. These collateral vessels can be coiled in the cardiac catheterization lab prior to transplant but with varying effectiveness.[15] Additionally, most failing Fontan patients present to transplant in poor metabolic and nutritional status. Being exposed to supraphysiologic central venous pressure can lead to protein-losing enteropathy, plastic bronchitis, ascites and edema. Steroids are often used to treat some of these sequelae and contribute to the overall deconditioned state going into surgery. Fontan patients can be deemed as failing due to actual cardiac dysfunction or may become transplant candidates due to the above associated problems in the face of preserved cardiac function.[16] The same technical considerations mentioned above used to deal with the SVC after bidirectional Glenn are relevant with the additional consideration of a foreshortened IVC. In patients who are large enough, a femoral venous cannula will allow for better utilization of remaining IVC.[13]

Donor evaluation

As mentioned previously in reference to waitlist mortality, there is a high degree of practice variability worldwide regarding cardiac donor acceptance. While this variability makes high-level recommendations difficult, the above-mentioned ISHLT consensus statement for donor acceptability highlights many important considerations. Donor cardiac function measured by echocardiographic LVEF seems to be the overall most important factor for acceptance and while a normal LVEF is generally universally acceptable, the group contends that a transiently decreased LVEF may be expected in brain death. The donor to recipient size matching is also quite variable. Some recipients, such as dilated or restrictive CM, deserve some tailoring of these criteria, but donor to recipient weight ratios from 0.6 to 3.0 have been reported to not be associated with worse outcomes. Most donors for pediatric heart transplants in North America are <35 years of age. There is evidence of accelerated allograft vasculopathy in donors of advanced age. Donor infections and comorbidities are always cautioned in donor evaluation, but few are absolute contra-indications. Many donor infections can be treated in a recipient. A non-inclusive list of especially concerning donor infections are: West Nile Virus, Trypanosoma cruzi, meningoencephalitis of unknown etiology and unrecognized fungal infections.[9]

Procurement

The anatomic variables present in transplanting CHD patients can impact the donor cardiectomy procedure – both in terms of donor tissue needed and timing of cross clamp of the donor heart. Donor structures that are commonly utilized for a congenital recipient include; entire donor aortic arch for aortic arch reconstruction, entire SVC and innominate vein for SVC reconstruction and branch PAs for PA reconstruction (if lungs are not being allocated). The PA and LA must be split with the lung team when the lungs have been allocated and there is little negotiation as both teams clearly need adequate tissue to anastomose. While the IVC length is similarly coveted by both heart and liver teams, division of this structure is generally not modifiable and should be divided at an agreed upon location at or near the diaphragm.[17]

Once all teams are ready for cross-clamping of the Ao, heparin is given and careful attention is made to completely decompress both sides of the heart to prevent distension with blood or preservation solution. There is some stylistic variability, but the LA can be vented by transecting a pulmonary vein or the LA appendage or by incising the LA at the anticipated site for eventual cardiectomy. The RA is vented by hemi-transection of the IVC. While infusing the preservation solution and ensuring adequate decompression, topical ice is applied to maintain hypothermia. After the infusion of preservation solution has completed, the heart is resected from the thoracic cavity by dividing the appropriate structures necessary for a particular case.[17] Cardiac decompression and hypothermia alone result in a 12-fold decrease in metabolic demand, but the preservation solution is needed to prevent cellular damage from various electrolyte and metabolic disturbances. There are many preservation solutions being used today with little consensus as to a single superior solution. Different studies have shown slight survival advantages with varying solutions such as University of Wisconsin solution and Histidine-Tryptophan-Ketoglutarate solutions.[18,19]

Minimizing donor ischemic time, or the time between cross-clamping of the Ao at the donor hospital and releasing the aortic cross-clamp after implantation, is imperative in cardiac transplant. Although isolated studies have demonstrated acceptable outcomes with ischemic times >6 h, it is generally felt that ischemic times < 6 h is best. Furthermore, a large (n=4716) retrospective analysis of pediatric heart transplant patients found that ischemic times <3.5 h was associated with improved outcomes.[9] Many factors are considered in order to minimize ischemic time. Travel time from donor hospital, sternal re-entry time in instances of previous operations and any significant procedures that will be done on the recipient between recipient cardiectomy and implant – such as aortic arch reconstruction or pulmonary arterioplasty are all considered. It is not uncommon, for these reasons, that a recipient surgeon will ask for a delay in donor cross-clamping to assure the ischemic time is minimized.[17] It should also be noted that the survival advantage seen in shorter cross clamp times may be confounded by the fact that many of the CHD patients having anatomic challenges that extend donor ischemic times, may have other factors (i.e. elevated pulmonary vascular resistance, sensitization) that impact survival.[9]

Post-operative management

The post-operative care of a pediatric heart transplant patients has some special considerations on top of standard practices.

Primary graft dysfunction (PGD) is a severe complication that is reported to occur in 2.4–28% of the pediatric population.[20,21] PGD occurs in the immediate postoperative period and is generally defined as significant (EF <40%) depressed ventricular function, need for high inotropic support, or need for mechanical support.[21] Studies have tried to determine the contributors leading to PGD. Results vary on significance but include donor characteristics of age and cause of death, recipient characteristics ofelevated pulmonary vascular resistance (PVR), organ dysfunction, ventilation and mechanical support and finally procedural variables including longer ischemic time and smaller center volume (<5).[20,21] Outcomes are poor, especially if mechanical support is needed for >4 days with one study showing a 100% mortality with extended ECMO and an overall 3-year survival of 54%.[21]

Therapy for high PVR and protective strategies for the right ventricle will have begun during the intraoperative period. It is essential to continue in order to try to avoid right ventricular failure which can be seen in up to half of the recipients and has been shown to be the cause of early death in 19%.[22,23] Contributors to right ventricular failure include pulmonary hypertension in the recipient, longer ischemic times and reperfusion injury. Therapies used for right heart dysfunction include: decreasing the PVR with inhaled vasodilators or O2, afterload reduction with milrinone, inotropic support, higher heart rate, and optimal fluid balance.[23]

Another unique aspect of post-operative heart transplant care is the lack of parasympathetic innervation; therefore, they lack the heart rate response to hypotension or hypovolemia. To achieve adequate heart rate, either isoproterenol working on adrenergic receptors and/or epicardial pacing is used. Once the patient's underlying rhythm is adequate, these strategies will be discontinued.

Immunosuppression is the other unique treatment needed after heart transplantation. The use of immunosuppression is broken into two phases: induction (given at the time of transplant) and maintenance therapy (given for life). There are many regimens and approaches to immunosuppression which vary by centers and age of the recipient. Regardless of which regimen is used, the patient will require additional monitoring in the early post transplant period associated with the drug selection.

Outcomes

There are many complications that can happen after heart transplantation, with the major ones being rejection, infection and forms of cancer. The multidisciplinary heart transplant team follows the patient with specific protocols to monitor for all these issues and intervene and reverse/treat them if possible. Due to these complications, patients may die or require multiple transplants.

Outcomes at 1 year and 5 years have improved when comparing 1982–1991 (1 year= 72.1%; 5 year 60.6%) to 2010–2017 (1 year= 91.5%, 5 year= 83%) (eSlide 35). Based on data from 2002 to 2009 the current 10-year survival is 68% with 15-year survival at 58.9% (eSlide 35). Looking at 10-year survival by age categories, patients transplanted between the ages of <1–10-years old had no statistical difference in survival, with an average between 83% and 85% (eSlide36). There is however, a statistical difference between all of these age groups and those patients 11–17 years old with a 10-year survival of this group of 70.2% (eSlide 36). When broken down by age group survival over era, all age groups survival statistics have improved (eSlide 37). Comparing outcomes across ages based on etiology of the transplant, those patients with DCM had higher survival, with DCM 1-year survival of 91–93% versus CHD at 82–88% (eSlide 43–46). Outcomes are also greatly affected by the need and type of mechanical support while waiting for an organ. The 5-year survival for patients who needed no mechanical support or those who needed only a VAD or total artificial heart (TAH) had improved outcomes (85%) than those who needed ECMO (77%).(eslide 51)

Pediatric heart transplantation is a specialized patient population that has unique preoperative, intraoperative and postoperative aspects that continue to evolve over time. With constantly evolving testing, support options and medications, the future holds many promising options for this fragile patient group.

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