Review Article

Donor considerations in pediatric heart transplantation

Nikki Singh, Muhammad Aanish Raees, Farhan Zafar

The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Contributions: (I) Conception and design: F Zafar; (II) Administrative support: F Zafar; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Farhan Zafar, MD. Assistant Professor, Department of Surgery, The Heart Institute, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave., Cincinnati, OH 45229, USA. Email: farhan.zafar@cchmc.org.

Abstract: Donors for pediatric heart transplantation are accepted based on variety of donor factors. There is wide variability in practice across centers and lack of evidence to guide standardized approach for some donor characteristics. This article reviews current practice and evidence for donor evaluation in pediatric heart transplantation.

Keywords: Donor evaluation; pediatric heart transplantation

Submitted Aug 10, 2019. Accepted for publication Aug 16, 2019.
doi: 10.21037/tp.2019.08.02
View this article at: http://dx.doi.org/10.21037/tp.2019.08.02

Pediatric heart transplant is used as a next step in palliation for children with heart failure refractory to other medical therapy. Current outcomes of all pediatric patients who undergo transplant has improved significantly since the initial transplant in 1967. In the current era, the 1- and 5-year survival are approximately 90% and 80%, respectively (1). However, the waitlist mortality continues to remain high. An analysis of the US Scientific Registry of Transplant Recipients (SRTR) database demonstrated that the overall 1-year mortality for all listed patients while waiting was 17% (2).

The size of the active waitlist for pediatric patients increased by >20% between 2010 and 2014 (3). As the number of patients placed on the transplant waitlist continues to grow, the number of pediatric heart transplant has been steady during this time (4). As a result, the percentage of patients transplanted among those on the waitlist has continued to decline. When looking at organ utilization in the same era, only 32% of all available donors and approximately 50% of pediatric donors were used for heart transplantation in 2014 (5).

Donor characteristics are used to determine acceptance of organs. Historically donor characteristics such as decreased ejection fraction, presence of cardiopulmonary resuscitation (CPR), prolonged CPR, predicted prolonged ischemic time, mechanism of death were thought to signify "marginal donors". This term is used to qualify donors who have characters which may lead to poor recipient outcomes. However, there is not enough evidence to substantiate such beliefs, and more recently, organ utilization has been evaluated further in hopes to expand the donor pool in order to match the growing waitlist (6-9). Furthermore, when looking at donor offers declined for organ quality, pediatric recipients that received hearts refused multiple times by other centers had similar outcomes to those recipients who had none or fewer refusals, even for the high-risk recipients (10).

In this review, we will discuss factors that are commonly reviewed when considering a donor offer for pediatric heart transplantation, in the light of recent literature.

Donor age

Donor age is considered a risk factor of poor post-transplant outcomes in the adult heart transplant field (11). However, when reviewing older donor offers the decision is likely dictated by comorbidities typically seen in the older population (e.g., coronary artery disease, and smoking history). Although possible, these comorbidities are uncommon in pediatric field. A recent study by Westbrook

et al. studied outcomes stratified by donor-recipient (D-R) age difference. They showed that a D-R age difference of >5 years was associated with decreased post-transplant survival, and increased coronary allograft vasculopathy. Of note, the increase in mortality was primarily contributed by the adolescent cohort receiving a donor heart from individuals >25 years of age (12).

Donor size—weight/ height/ BSA or virtual fit

The donor-recipient body weight (DRWB) ratio is the most common method to determine acceptable donor weights for recipients, which among other factors creates a range for possible donor offers for the candidates. This ratio does not incorporate actual cardiac volumes, which has shown to limit possible donors. More strikingly, these DRWB ratio vary significantly from program to program and even within a program without any consistency (13,14).

More recently the concept of virtual fit using 3D printing has emerged as a tool to continue to expand possible donors. A recent study by Szugye *et al.* compared their standard donor-recipient body weight-based listing (1:1 to 1.5:1) to chest computed tomography scans (CTs) of dilated cardiomyopathy patients which had been obtained as part of routine imaging prior to transplant and then later converted to 3D imaging analysis. They found that virtual transplantation was able to allow for a wider range of weights when compared to their standard weight-based listing, overall allowing for individualized size matching (15).

Additional work done by Plasencia *et al.* used virtual fit to aid clinicians in predicting potential compression effects from donor offers, with the goal to expand potential donor offers by accepting "oversized" donors (16). Two methods were used: First was a healthy heart library to derive a suitable donor to match the organ offer and the second method utilized actual donor images to create a real-time 3D visual assessment of fit. The heart health library used linear regression model of normal heart reconstructions offers based on CT/MR images to determine total cardiac volume (TCV) to develop and validate a linear regression model that predicts a healthy allograft TCV. They reported a total of 3 cases, where DRBW ratio was in the range of 2–3 (unacceptable in many programs); however, the actual TCV ratio was 1 or less and their program proceeded with transplant without any complications. These studies and other current efforts in the field will provide standardized, evidence-based tools that could determine "safe" upper limits of potential donor size and move away from an archaic method of predicting appropriate cardiac size.

Mechanism/cause/circumstance of death

Donors' mechanism or cause of death is generally not a concern where complete information about organ function and anatomy is available. However, situations with incomplete cause of death data still exist: in blunt trauma victims where, cardiac contusion cannot be ruled due to insufficient imaging or laboratory data, or transmittable disease status (especially HIV) in drug over dose cases to just describe a few. In such situations, decisions are dictated by recipient factors, likelihood of waitlist survival, and the assessment of donor retrieval teams. Of note, cases where the cause of death is unknown, such as in the case of an otherwise healthy child who was found unresponsive (SUID), careful cardiac and genetic considerations are warranted to ensure successful transplantation.

CPR and duration of CPR have been a point of contention among providers making decisions about donor offers (13). Several studies have demonstrated that the presence and duration of CPR have no influence on short- or long-term posttransplant outcomes (17-19). Of note, these studies did not analyze all donors resuscitated beyond 30 minutes in their study population. Therefore, any resounding conclusions regarding the effect of extended CPR on posttransplant outcomes are challenging to make.

Ejection fraction

Similar to general practice, normal ejection fraction is commonly defined at ≥55% for donor hearts. This information is reviewed and is a significant part of decision making at the time of donor offer. Donors with reduced ejection fraction have been cautiously used in pediatric patients due to the belief that decreased ejection fraction implies poor organ function and may cause poor transplant outcomes. However, it is important to realize that echocardiographic evaluation is generally performed in a setting where cardiac function is influenced by an "autonomic storm" secondary to brain death. This is commonly referred to as "neurogenic stress cardiomyopathy in heart donors" (20). In these cases, a depressed left ventricular (LV) function is likely transient in an otherwise healthy individual. This phenomenon was demonstrated by Madan *et al.* in a study that compared donor hearts with transient left ventricular systolic dysfunction (measured on multiple echocardiograms during donor management)

with donors with normal LV function at baseline. This study primarily studied the adult population but found that the group with transient LV dysfunction was significantly younger (median age of 25 *vs.* 30). Post-transplant outcomes were similar in terms of 30-day, 1, 3, and 5 years mortality (21). These findings were supported by other similar studies (22).

In pediatric heart transplantation, literature regarding the effect of low ejection fraction has been inconsistent. Some studies reported low ejection fraction as an independent predictor of post-transplant 1-year mortality whereas, a study by Rossano *et al.* found that recipients who received hearts with depressed function had similar outcomes to those whose donors had a normal ejection fraction, regardless of the degree of dysfunction (8,23). A consistent finding from these studies was that donors with sub normal ejection fractions were rarely utilized.

Even with studies showing similar outcomes despite donor LV dysfunction, a high percentage of organs are still not utilized. UNOS review from 2007 to 2014 of donors between 13 to 58 years of age showed that about 20% of potential cardiac donors are excluded due to LV dysfunction (24). Given the increasing literature showing similar outcomes of recipients who receive heart donors with reduced ejection fraction, there is a potential to significantly expand the donor pool and therefore decrease waitlist mortality.

ABO incompatible

Infants and children often have longer waitlist time compared to older children given limited donor availability for their size and age, even when listed as highest priority for an organ. Generally, blood types must be matched between recipient and donors. One advantage in young infants and children however is the presence of an immature immune system and their inability to produce adequate levels of isohemagglutinins (anti-A or anti-B) until the age of 12 to 14 months. This allows for the option to accept hearts across blood types. As a result, centers have been using ABO incompatible (ABOi) heart transplants to optimize donor options. The first ABOi transplant was performed in an infant in Canada in 1996 (25). Since then studies continue to show equivalent outcomes in infants and young children who receive an ABOi heart transplant and similar freedom from rejection when compared to ABO compatible transplants (26,27). Given these comparable outcomes, more countries are using the option of ABOi heart transplantation.

Most centers perform isohemagglutinin testing in the recipient to assess the presence and concentration of antibodies toward other blood types. Acceptable antibody titers for transplanting across blood groups is <1:16, as recommended by UNOS policy (28). Some centers have reported ABO incompatible transplants with titers ≥1:16. In the United Kingdom, where transplantation across blood types has been performed for longer than in the United States, a report of 12 patients (five of which were >2 years of age) had isohemagglutinin titers of ≥1:16 and were transplanted. Thirty-three percent of these patients had early anti-body mediated rejection within the first 15 days after transplant. Three of the 12 patients died; however, these deaths were not believed to be directly related high isohemagglutinin titers. In regards to overall survival, there was 75% survival in the high titer group versus 89% survival in patients with <1:16 titers (29). The results from ABOi transplants provide careful optimism for a difficult to match recipient population and its broadening use require further investigation.

Positive crossmatch

All individuals have a unique set of human leukocyte antigens (HLAs) which are expressed on their tissue and organs, and allow the immune system to recognize self from non-self. Prior to listing for transplant, each recipient is evaluated for antibodies against non-self HLAs. This process of evaluating for antibodies against possible donors in the general community is called panel reactive antibodies (PRAs). If there are preformed antibodies toward potential donors in the community then those donors are avoided in order to prevent hyper-acute and acute rejection of the heart following transplant. If a recipient has a high percentage of PRAs then they are considered sensitized (often >10% is considered sensitized), which is a challenge as it can exclude multiple potential donor options. As a result, children who are sensitized have a longer waitlist duration and increased waitlist mortality (30,31).

Some transplant centers may transplant organs in which the recipient has known antibodies towards a donor, this is known as a positive crossmatch. Outcomes of patients who undergo positive crossmatch have shown higher risk of post-transplant mortality. A review of the UNOS data registry showed that an elevated PRA was associated with overall worse post-transplant mortality (32). Further study by the clinical trials in organ transplantation in children

(CTOTC) program used a prospective, multi- institutional observational cohort study design to assess the impact of pretransplant sensitization. A total of 54% were considered sensitized by their criteria and were found to have less freedom from acute antibody mediated rejection as well as cellular rejection. However, freedom from death, re-transplantation or rejection with hemodynamic compromise at 12 months were comparable (33).

The question remains, what are acceptable outcomes for transplant in this setting and when is it worth the risk to perform a positive cross match transplant? More work is needed in this area to determine the safety of these types of transplant and their impact on outcome in the immediate post-transplant course and more importantly in the long term.

Ischemic time

Longer donor ischemic time is shown to have significant impact on post-transplant morbidity and survival (23,34,35). Offers where expected ischemic times are greater than 4 hours usually encourage teams to carefully consider other recipient factors such as chances of waitlist survival, diagnosis, etiology of cardiac decompensation, presence of PRA, donor-CPR time, and ejection fraction in their decision making. Additionally, it also informs the decision to increase the frequency of post-transplant surveillance. Furthermore, there is growing evidence about the use of ex-vivo perfusion for supporting organs with prolonged ischemic time and can potentially reduce or eliminate this consideration in the future (36).

Donor scoring systems

In the current system, donor evaluation is largely a subjective and qualitative process. In contrast, kidney transplantation follows a highly quantitative method of evaluating multiple donor factors using standardized tools such as the kidney donor risk index (KDRI), which not only informs decision making but has shown to positively impact outcomes (37). There is a significant amount of variability in donor acceptance practices at different pediatric heart transplant centers which contributes to poor donor utilization and makes studying outcomes challenging (38). Several groups have made strides toward developing a tool that could address this issue; however, it needs further improvement and validation to be introduced into practice (23,39). Another concept that is being studied by our group is whether a risk-based donor and recipient matching will allow for better organ utilization and improve the total number of post-transplant years achieved for the entire transplant population.

Donor evaluation for heart transplantation is a complex multi-step process and requires consideration of many recipient and donor factors, some of which are not discussed here. Given the growing waitlist, donor shortage is a cause for concern and the transplant community is increasingly focused on methods to improve donor utilization, which could mean expanding some of the criteria discussed above.

Acknowledgments

Funding: This work is funded in part by NIH (R01 HL147957 01).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Rossano JW, Dipchand AI, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Heart Transplantation Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. J Heart Lung Transplant 2016;35:1185-95.
2. Almond CS, Thiagarajan RR, Piercey GE, et al. Waiting list mortality among children listed for heart transplantation in the united states. Circulation 2009;119:717-27.
3. Colvin M, Smith JM, Skeans MA, et al. OPTN/SRTR 2014 Annual data report: heart. Am J Transplant 2016;16:115-40.
4. Colvin M, Smith JM, Hadley N, et al. OPTN/SRTR 2016 Annual Data Report: Heart. Am J Transplant 2018;18:291-362.
5. Organ Procurement and Transplantation Network. National data. Available online: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/

6. Zafar F, Rizwan R, Lorts A, et al. Implications and outcomes of cardiac grafts refused by pediatric centers but transplant by adult centers. J Thorac Cardiovasc Surg 2017;154:528-36.e1.
7. Conway J, Chin C, Kemna M, et al. Donors' characteristics and impact on outcomes in pediatric heart transplant recipients. Pediatr Transplant 2013;17:774-81
8. Rossano JW, Lin KY, Paridon SM, et al. Pediatric heart transplantation from donors with depressed ventricular function: an analysis of the United Network of Organ Sharing Database. Circ Heart Fail 2013;6:1223-9.
9. Morrison AK, Gowda C, Tumin D, et al. Pediatric marginal donors hearts: Trends in the US national use, 2005-2014. Pediatr Transplant 2018;22:e13216.
10. Rizwan R, Zafar F, Bryant R III, et al. The number of refusals for donor organ quality does not impact heart transplant outcomes in children. Ann Thorac Surg 2018;105:1223-30.
11. Lund LH, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-second Official Adult Heart Transplantation Report—2015; focus theme: early graft failure. J Heart Lung Transplant 2015;34:1244-54.
12. Westbrook TC, Morales DL, Khan MS, et al. Interaction of older donor age and survival after weight-matched pediatric heart transplantation. J Heart Lung Transplant 2017;36:554-8.
13. Godown, J, Kirk R, Joong A, et al. Variability in donor selection among pediatric heart transplant providers: Results from an international survey. Pediatr Transplant 2019;23:e13417.
14. Riggs KW, Giannini CM, Szugye N, et al. Time for evidence-based, standardized donor size matching for pediatric heart transplantation. J Thorac Cardiovasc Surg 2019. [Epub ahead of print].
15. Szugye NA, Lorts A, Zafar F, et al. Can virtual heart transplantation via 3-dimensional imaging increase the maximum acceptable donor size? J Heart Lung Transplant 2019;38:331-33.
16. Plasencia JD, Kamarianakis Y, Ryan JR, et al. Alternative methods for virtual heart transplant-Size matching for pediatric heart transplantation with and without donor medical images available. Pediatr Transplant 2018;22:e13290.
17. Cheng A, Schumer EM, Trivedi JR, et al. Does donor cardiopulmonary resuscitation time affect heart transplantation outcomes and survival? Ann Thorac Surg 2016;102:751-8.
18. Khan MS, Karani KB, Zafar F, et al. Does duration of donor cardiopulmonary resuscitation impact pediatric cardiac graft survival? J Heart Lung Transplant 2014;32:S42.
19. Quader MA, Wolfe LG, Kasirajan V. Heart transplantation outcomes from cardiac arrest-resuscitated donors. J Heart Lung Transplant 2013;32:1090-5.
20. Madias JE. "Neurogenic stress cardiomyopathy in heart donors" is a form of Takotsubo syndrome. Int J Cardiol 2015;184:612-13.
21. Chen CW, Sprys MH, Gaffery AC, et al. Low ejection fraction in donor hearts is not directly associated with increased recipient mortality. J Heart Lung Transplant 2017;36:611-615.
22. Madan S, Saeed O, Vlismas P, et al. Outcomes after transplantation of donor hearts with improving left ventricular systolic dysfunction. J Am Coll Cardiol 2017;70:1248-58.
23. Zafar F, Jaquiss RD, Almond CS, et al. Pediatric Heart Donor Assessment Tool (PH-DAT): A novel donor risk scoring system to predict 1-year mortality in pediatric heart transplantation. J Heart Lung Transplant 2018;37:332-9.
24. Tryon D, Hasaniya NW, Jabo B, et al. Effect of left ventricular dysfunction on utilization of donor hearts. J Heart Lung Transplant 2018;37:349-57.
25. West LJ, Pollock-Barziv SM, Dipchand AI, et al. ABO-incompatible heart transplantation in infants. N Engl J Med 2001;344: 793-800.
26. Dipchand AI, Pollock BarZiv SM, Manlhiot C, et al. Equivalent outcomes for pediatric heart transplantation recipients: ABO-blood group incompatible versus ABO-compatible. Am J Transplant 2010;10:389-97.
27. Henderson HT, Canter CE, Mahle WT, et al. ABO-incompatible heart transplantation: Analysis of the Pediatric Heart Transplant Study (PHTS) database. J Heart Lung Transplant 2012;31:173-9.
28. United Network for Organ Sharing (UNOS) Policy 2019, Section 6.6.B Eligibility for Intended Blood Group Incompatible Offers for Decreased Heart Donors. Available online: https://optn.transplant.hrsa.gov/governance/policies/
29. Irving CA, Gennery AR, Carter V, et al. ABO-incompatible cardiac transplantation in pediatric patients with high isohemagglutinin titers. J Heart Lung Transplant 2015;34:1095-102.
30. Feingold B, Bowman P, Zeevi A, et al. Survival in all sensitized children after listing for cardiac transplantation.

J Heart Lung Transplant 2007;26:565-71.
31. Feingold B, Young Park S, Comer DM, et al. Outcomes after listing with a requirement for a prospective crossmatch in pediatric heart transplantation. J Heart Lung Transplant 2013;32:56-62.
32. Mahle WT, Tresler MA, Edens RE, et al. Pediatric Heart Transplant Study Group. Allosensitization and outcomes in pediatric heart transplantation. J Heart Lung Transplant 2011;30:1221-7.
33. Webber S, Zeevi A, Mason K, et al. Pediatric heart transplantation across a positive crossmatch: First year results from the CTOTC-04 multi-institutional study. Am J Transplant 2018;18:2148-62.
34. Magdo HS, Friedland-Little JM, Yu S, et al. The impact of ischemic time on early rejection after pediatric heart transplant. Pediatr Transplant 2017;21. doi: 10.1111/petr.13034.
35. Rodrigues W, Carr M, Ridout D, et al. Total donor ischemic time: relationship to early hemodynamics and intensive care morbidity in pediatric cardiac transplant recipients. Pediatr Crit Care Med 2011;12:660-6.
36. Chan JL, Kobashigawa JA, Reich HJ, et al. Intermediate outcomes with ex-vivo allograft perfusion for heart transplantation. J Heart Lung Transplant 2017;36:258-63.
37. Stewart DE, Kucheryavaya AY, Klassen DK, et al. Changes in deceased donor kidney transplantation one year after KAS implementation. Am J Transplant 2016;16:1834-47.
38. Park CS, Villa CR, Lorts A, et al. Is there an optimal organ acceptance rate for pediatric heart transplantation: "a sweet spot"? Pediatr Transplant 2018;22:e13149.
39. Fraser CD 3rd, Grimm JC, Zhou X, et al. Children's Heart Assessment Tool for transplantation (CHAT) score: a novel risk score predicts survival after pediatric heart transplantation. World J Pediatr Congenit Heart Surg 2019;10:296-303.

Cite this article as: Singh N, Raees MA, Zafar F. Donor considerations in pediatric heart transplantation. Transl Pediatr 2019;8(4):284-289. doi: 10.21037/tp.2019.08.02