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Part IV: Effects of Donor Cause of Death, Ischemia Time, Inotrope Exposure, Troponin Values, Cardiopulmonary Resuscitation, Electrocardiographic and Echocardiographic Data on Recipient Outcomes: A Review of the Literature

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Abbreviations: VAD- Ventricular Assist Device; CPR- Cardiopulmonary Resuscitation; ECG- Electrocardiogram; CVA- Cerebrovascular Accident HIV- Human Immunodeficiency Virus; HCV- Hepatitis C Virus; OPTN- Organ Procurement and Transplantation Network; UNOS- United Network of Organ Sharing; SIDS- Sudden Infant Death Syndrome; BNP- Brain Natriuretic Peptide; DIT- Donor Ischemic Time; CHD- Congenital Heart Disease; OCS- Organ Care Systems; LVEF- Left Ventricular Ejection Fraction; LVH- Left Ventricular Hypertrophy

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Abstract

Background: Heart transplantation has become standard of care for pediatric patients with either end-stage heart failure or inoperable congenital heart defects. Despite increasing surgical complexity and overall volume, however, annual transplant rates remain largely unchanged. Data demonstrating pediatric donor heart refusal rates of 50% suggest optimizing donor utilization is critical. This review evaluated the impact of donor characteristics surrounding the time of death on pediatric heart transplant recipient outcomes.

Methods: An extensive literature review was performed to identify articles focused on donor characteristics surrounding the time of death and their impact on pediatric heart transplant recipient outcomes.

Results: Potential pediatric heart transplant recipient institutions commonly receive data from 7 different donor death related categories with which to determine organ acceptance: cause of death, need for cardiopulmonary resuscitation, serum troponin, inotrope exposure, projected donor ischemia time, electrocardiographic and echocardiographic results. Although donor ischemic times up to 8 hours have been reported with comparable recipient outcomes, most data support minimizing this period to less than 4 hours. Cerebrovascular accident as a cause of death may be associated with decreased recipient survival but is rare in the pediatric population. Otherwise, however, in the setting of an acceptable donor heart with a normal echocardiogram, none of the other data categories surrounding donor death negatively impact pediatric heart transplant recipient survival.

Conclusions: Echocardiographic evaluation is the most important donor clinical information following declaration of brain death provided to potential recipient institutions. Considering their relative importance, every effort should be made to allow direct image visualization.

Introduction

Orthotopic heart transplantation has become standard of care for the pediatric population with either end stage heart failure or inoperable congenital heart defects, in part due to median post-transplant survival of greater than 15 years. [1] Although ventricular assist devices (VAD) have improved recipient candidacy and utilization of ABO incompatible donors have allowed for shorter wait times in younger infants, approximately 20% of all potential pediatric recipients die or are removed from the waitlist prior to transplantation. [2,3]

Pediatric cardiac surgical volume has increased markedly over the past decade[4] while pediatric heart transplantation rates have largely plateaued between 500 and 600 annually. [5] While some of this discrepancy is due to post-surgical survival rates approaching 97%,[4] a likely larger component is the nearly 50% discard rate of available pediatric donor hearts. [6] Optimizing donor organ management and subsequent organ utilization requires increased attention.

A better understanding of donor characteristic significance is critical to improve organ utilization, minimize waitlist time and mortality, and optimize post-transplant survival. The objective of this manuscript is to determine the relative impact of the following donor characteristics on recipient survival: cause of death, troponin and other cardiovascular biomarkers, ischemia/ travel time, inotropic therapy, need for and duration of cardiopulmonary resuscitation (CPR), electrocardiographic (ECG) findings, and echocardiographic findings.

Methods

This review was developed by searching the MEDLINE, Cochrane Library and Web of Science databases in October 2018 with the help of a medical librarian. Index terms and keywords included heart transplantation, donor selection, tissue and organ procurement, utilization, survival, waitlist, refusal, mortality, morbidity, allocation, electrocardiogram, echocardiogram,

and pediatric. The search was limited to the English language and year greater than 2009. The reference lists of studies selected for inclusion were scanned for relevant articles. A hand search of known articles was also included. After removing duplicates, 1475 articles remained.

Donor Cause of Death

Cause of death is commonly the first data discussed when considering a potential organ donor. Excluding donation after cardiac death, two major etiology categories arise: non-transferrable and potentially transferrable causes. Non-transferrable causes of death include disease mechanisms leading to irreversible brain damage such as trauma, asphyxia and cerebrovascular accidents (CVA) while potentially transferrable causes of death are comprised of infectious diseases and malignancy. The relative impact of these two categories on recipient outcomes has received considerable attention in both the pediatric and adult literature.

Pathologic intracranial pressure elevations progressively decrease cerebral perfusion pressure and result in cerebral ischemia. Compensatory responses from the central nervous system result in supra-physiologic surges in catecholamines, sympathetic nervous system output, systemic vascular resistance, and both sodium and water retention in attempts to increase systemic pressures and maintain adequate cerebral perfusion. [7] Unabated, this response progresses to cerebral ischemia, brainstem herniation, and brain death. During this systemic autonomic 'storm', the commensurate increases in myocardial preload, afterload, contractility, heart rate and oxygen demand are similarly profound and can produce significant ventricular dysfunction. [8,9]. Immediately following brainstem herniation, however, there is complete deactivation of the sympathetic nervous system and commonly a significant injury to the ischemia-prone hypothalamic-pituitary axis. This shift suddenly removes all the catecholamine, thyroid hormone, cortisol, vasopressin and sympathetic nervous system output that were simultaneously straining the myocardium but maintaining end organ perfusion. The resulting physiology is typically characterized by decreased contractility, low systemic vascular resistance, and diabetes insipidus. When such patients become organ donors, they are subsequently managed with a variety of fluid repletion, anti-diuretic hormone, inotropes,

vasopressors and hormone repletion which have the potential to mimic the initial period of brainstem herniation. It is at this point that potential recipient institutions must determine whether such injuries are likely to affect recipient outcomes. Further complicating this decision is the significant up-regulation of inflammatory cytokines accompanying brain death and the theoretical risk of an ischemia/ reperfusion injury, rejection and primary graft dysfunction they may incite immediately following transplantation. [8,10]

Data surrounding organ use from donors with the different types of non-transferrable causes of death are mixed. Several adult studies have demonstrated no association between cause of death and recipient/ graft survival[11,12] but others found CVA to be associated with worse outcomes.[13] However, the association between CVA and worse outcomes may be related to the increased incidence of hypertension, diabetes mellitus, and tobacco use in donors dying from CVA.[11,14] The data in pediatric and young adult populations, where CVA is clearly an uncommon cause of death, is similarly mixed. Some studies suggest that CVA as the donor cause of death is associated with slightly higher 1-year mortality rates following transplantation,[15,16] but others have not. [17-19] While it is plausible that the association between donor CVA and subsequent post-transplant mortality differs between adults and children, there is insufficient data to support this assertion. Unfortunately, there is even less data on other non-transferable causes of donor death. Although anecdotal concerns have been expressed regarding the use of donors dying from either smoke inhalation or drowning, there is inadequate data to specifically address these issues.

Transmission of pathogenic microorganisms from donor to recipient is a constant source of concern for transplant centers. This heightened sense of awareness is further exacerbated by the recipient's impending immunosuppressed status and when a pathogen was the donor's cause of death. However, successful transplantation of non-lymphoid organs such as the heart (as compared to lungs and intestines) have occurred from both pediatric and adult donors infected with influenza, [20-22] bacterial meningitis, [23] and bacteremia[24,25]. The use of such organs, often with anti-microbial therapy in both the donor and recipient, is supported by the American Society of Transplantation Infectious Disease Community of Practice. [26] Despite these

recommendations, however, actual utilization of such 'high risk donors' is uncommon in the pediatric population, accounting for only 4.1% of all pediatric transplantations. [27] Considering the overall 50% discard rate of potential pediatric donor hearts, it is not surprising that acceptance of human immunodeficiency virus (HIV) or hepatitis C (HCV) positive donor organs is negligible, despite no reported cases of recipient HIV transmission and recent medication regimen effectively eradicating HCV in adults receiving organs from HCV infected donors. [28] Of note, presumably in part due to low transmission rates, approximately ¾ of respondents in a recent international survey of pediatric heart transplant physicians said they would accept organs from infants exposed to known or suspect HIV or HCV infected mothers. [29]

Although far less common, donors with active or prior malignancy history are another potential source for organ donation with disease transmission. The largest study assessing this risk evaluated over 8,000 potential Chinese donors across all age ranges with a positive cancer history resulting in over 700 organ transplants. [30] While there was no increased incidence of cancer transmission, they found significantly worse survival in heart transplant recipients from donors with either hematologic or otorhinolaryngologic cancers but not with central nervous system tumors. A similar lack of tumor transmission was found in a smaller adult study including only 3 heart transplantations. [31]

The overall paucity of data on this subject prompted the OPTN/ UNOS to establish a Disease Transmission Advisory Committee tasked with producing guidelines on organ acceptance from donors with a positive malignancy history. Their document recommended employing a strategy of utilizing anticipated donor malignancy recurrence-free survival or 'cure' rates as a surrogate marker for transmission risk. 'Low risk' would be expected from donors who are cancer free for at least 5 years with a cure probability of cure >99%; 'intermediate risk' would be those with a 90-99% cure rate; and 'high risk' would be associated with incurable cancers, insufficient follow up or cure probability <90%.[32] Additional consideration should be given to the metastatic potential of the donor's current or prior malignancy. In general, however, considering the overall limited data and near absence in the pediatric population, there is insufficient data to make any meaningful recommendations for the pediatric donor with a history of or active malignancy.

Donors with an unrecognized cause of death pose another specific challenge for organ transplantation. Considering the significant electrocardiographic abnormalities associated with the brain death induced electrolyte and neurohormonal changes, [33] it may be impossible to definitively exclude a channelopathy in patients with unknown cause of death. A similar concern is the neonatal donor dying from Sudden Infant Death Syndrome (SIDS). However, a small study demonstrated heart transplantation from SIDS donors with normal ejection fraction had outcomes comparable to non-SIDS donors. [34]

Donor Troponin and Other Biomarkers

Serum biomarkers of donor myocardial cell death are commonly elevated immediately after cardiopulmonary resuscitation or the catecholamine surge accompanying brainstem herniation. While values such as troponin and creatinine kinase-myocardial band (CK-MB) are theoretically attractive due to their wide availability and myocardial specificity, [35] it is important to understand their actual utility in potential donor heart selection.

Troponin-I and troponin-T are sensitive and specific to myocardial injury and are routinely obtained in both pediatric and adult donors. However, both isoforms can remain elevated for several days after an injurious event has terminated, [35] significantly complicating their interpretation. A Eurotransplant database study of 774 adult recipients demonstrated elevated donor troponin values, but not CK-MB values, to be associated with decreased 3 year survival. [36] By comparison, a single center adult study of 159 potential heart donors demonstrated higher troponin values to be associated with an increased incidence of segmental wall motion abnormalities and lower ejection fractions but not with 1-year recipient survival. [37] Considering the average ejection fraction of donor hearts ultimately harvested for transplant was >60%, these data suggested troponin to be associated with acute myocardial injury but not with potential for recovery or recipient outcomes.

This assertion is widely supported in the adult literature. Two UNOS database studies of approximately 11,000 adult donors in which the first assessed all organs with normal ejection fractions and found no association between troponin values and recipient outcomes and a

second in which 472 recipients received hearts with a median initial ejection fraction of 35% but normalized prior to transplant, similarly found no association between troponin values and recipient outcomes. [38,39] Several other smaller adult studies have demonstrated elevated troponin values to be associated with left ventricular dysfunction on initial echocardiograms but not with recipient survival[40,41] or primary graft dysfunction. [42]

Only two pediatric studies have addressed the association between myocardial injury biomarkers and recipient outcomes. A large, single center pediatric cohort of 182 heart transplant recipients demonstrated no correlation between final troponin or CK-MB values and recipient outcomes, though all donor echocardiograms exhibited normal function prior to transplant. [17] An OPTN database study of 657 heart transplant recipient <21 years of age similarly demonstrated no association between final donor troponin value and recipient outcomes and instead recommended a practice of determining troponin trends and timing from declaration of brain death. [43]

Several small studies of both pediatric[44] and adult donors[45-47] have failed to demonstrate the utility of BNP and NT-proBNP values in predicting recipient outcomes but some have shown weak correlations with early myocardial dysfunction. [45,47]

Donor Ischemia/Travel Time

Donor allograft ischemic time (DIT) is defined as the time elapsed between aortic cross-clamp during organ procurement and coronary artery reperfusion during heart implantation. This topic has received a great deal of attention in the pediatric population and was a 2017 ISHLT registry report focus. The most commonly reported mean DIT in pediatric heart transplantation is approximately three and a half hours; although ranges have extended to 10 hours, DIT >6 hours remains unusual. [48-52] In a recent survey describing donor acceptance practices of pediatric heart transplant clinicians, 45% of respondents said they would accept a donor heart with DIT <4 hours, 22% up to 5 hours, and another 33% would accept up to 6 hours DIT. [29] Several of the larger registry-based studies have noted longer DIT to be related to younger age, [48,50,52] diagnosis of congenital heart disease (CHD), [48,50,52] mechanical circulatory support[52] and

higher acuity. [48,52] Longer DIT has also been described outside of North America, though reporting has been variable. [52]

DIT >4 hours has been associated with increased intensive care unit and hospital stay[51,52] and need for mechanical ventilator support, [51] but has not been demonstrated to impact rejection or coronary graft vasculopathy. [52] In the majority of studies, longer DIT is associated with primary graft failure, [15,48,50,52-55] but not long-term graft or recipient survival. [15,48-50,52,54-56] Subgroup analyses have demonstrated conflicting age-related effects of DIT on outcomes, [49,50,52,54] with some concluding adolescence to be the highest risk period[50,54] while others found worse outcomes in infants. [52]

DIT is one of the most commonly cited parameters used to determine outcomes in the first year after heart transplant. A large retrospective cohort of pediatric heart transplant recipients (n=4,716) spanning over 2 decades demonstrated significantly improved 1-year survival in those with DIT <3.5 hours . [48] The 2017 ISHLT registry report found DIT >4 hours was independently associated with decreased survival at both 1 (87% vs. 92%) and 5 years (77% vs. 82%) post-transplant, but the effect was no longer present at 10 or 15 years; there was no long-term effect on morbidity. [52]

It must also be recognized that although DIT is a convenient, objective variable for evaluation, it is comprised of several confounding components. CHD patients following multiple sternotomies commonly require prolonged explant times, producing unforeseen technical challenges. Subsequent survival differences may be attributable to recipient factors rather than issues surrounding donor distance or travel time. Further, while there is an obvious direct relationship between DIT and travel time, they are not identical and the correlation between the two is often poor. One large retrospective adult study of over 14,000 transplants demonstrated that when accounting for DIT, transplant center volume, and both recipient and donor characteristics, a 7% reduction in mortality at 30 days and a 6% reduction in mortality at 1 year were noted for every 100-mile increase in donor-recipient distance; there were no distance related survival differences in unadjusted Kaplan-Meier curves. [57] Conversely, the authors did find DIT to be an independent predictor for mortality at both 30 days and 1 year, and they hypothesized that after controlling for the detrimental impact of prolonged DIT, there must be

a hidden, protective association between recipient survival and longer donor distances, which may be a surrogate for differences in myocardial cooling times or preservation practices. Certainly from the existent data, despite long DIT and travel distances, good outcomes can be achieved in both pediatric and adult recipients. [49,57]

Of note, some data from adult studies suggest that warm ischemic time (or surgical implant time) may have a more important impact on post-transplant outcomes than prolonged cold ischemic time. [58] However, surgical implant time is highly confounded with measures of recipient risk including a history of prior procedures, the need for concomitant procedures at the time of transplantation, and technical challenges with allograft implantation. No recommendations on what constitutes excessive warm ischemic time can be made, although it is prudent to reduce warm ischemia as much as practical.

A recent review provides biochemical comparisons between common preservation solutions and relevant preservation studies, but there have been no new developments in this area for a considerable time. [59] Hypothermia alone is unable to abolish all cellular damage as metabolism persists at approximately 5-10% of normal. The Organ Care Systems (OCS) is a potential solution, allowing prolonged (up to 8 hours) normothermic myocardial perfusion, but is currently only suitable for older teenagers due to instrumentation size. This technology is expanding potential geographic zones for organ procurement and reducing the detrimental effects of DIT due to unanticipated factors such prolonged explant times. [60,61]

Donor Cardiopulmonary Resuscitation

Cardiopulmonary resuscitation (CPR) is relatively common in organ donors, either leading to their brain death or as a result. The challenge this history presents for recipient institutions is the inherent warm ischemic time and its potential short- and long-term effects on recipient outcomes. Due to these theoretical concerns, hearts from CPR positive donors are routinely rejected. [14,17,62] Considering CPR positive donors comprise up to 40% of some pediatric series, [17] determining the relative importance of this information is paramount to expanding the available donor pool.

A Pediatric Heart Transplant Society (PHTS) study examining the effect of donor characteristics on outcomes of 3,149 recipients found no donor characteristics, including presence or absence of donor CPR, to have a negative effect on overall recipient outcomes. [50] Likewise, a 2011 study of pediatric heart transplant recipients using the United Network of Organ Sharing (UNOS) database found no effect of donor CPR on recipient survival at 30 days, 1-, and 5 years post transplant. [63] A recent systematic review came to similar conclusions, supporting consideration of transplant after donor CPR, citing these and 3 older studies specifically relevant to pediatric heart transplantation. [64] Data from several adult studies also support the use of donor hearts without consideration of CPR status. [36,65,66]

Interestingly, a single institution study from France actually found higher 5- and 10-year survival in their adult heart transplant recipients who received CPR positive donor hearts, prompting the authors to suggest donor myocardial ischemic preconditioning may have salutary effects. [67] This has been similarly demonstrated in a pediatric cohort. [63] It should be noted, however, that many of the studies promoting the use of CPR positive donors also demonstrate normal left ventricular ejection fraction (LVEF) in the entire cohort, [17,38,63,67] suggesting that echocardiographic measures of cardiac function are a more important factor in recipient outcome than whether or not CPR occurred. [16] Therefore, in the absence of data suggesting a negative association between donor CPR and recipient outcomes, its history, regardless of duration, should not preclude transplantation of an otherwise acceptable donor heart. [50,62-64,67]

Donor Inotrope Exposure

Following brainstem herniation, the body's neurohormonal response designed to maintain cerebral perfusion pressure is suddenly truncated. The result is a loss of sympathetic and adrenergic output producing a catecholamine, afterload and preload deficient state that must be mitigated if organs are to be preserved for donation. Inotrope infusions and fluid resuscitation comprise the majority of interventions undertaken to maintain adequate organ perfusion, but could theoretically induce permanent donor myocardial injury when used excessively. This concern has led some to define inotrope supported donor hearts as

'marginal'[68] and is a common indication for organ refusal. [69] Whether donor inotrope exposure actually alters pediatric heart transplant recipient outcomes is therefore of significant interest.

Studies suggesting a negative impact of donor inotropic exposure are rare. An adult study assessing high (>10 mcg/kg/min) verses low dose (<10 mcg/kg/min) donor dopamine exposure on recipient outcomes found a non-significant trend towards endomyocardial biopsy evidence of myocyte necrosis in the high dose group but no differences in donor ejection fraction, post-transplant ICU duration or 5-year recipient survival. [70] A Pediatric Heart Transplant Society (PHTS) model predicting 1 year post transplant survival using recipient or donor factors demonstrated a weak association between lower survival and 'higher donor vasoactive support', but only in recipients with congenital heart disease and only in a model that included both donor and recipient data. [18] The 2017 ISHLT registry report cited donor inotrope use to be associated with decreased 1-year post transplant survival in recipients less than 1 year, but without mention of number of inotropes, dosing or ventricular function. [52]

By comparison, the majority of studies assessing donor inotrope use have either shown no association with post-transplant outcomes[50,68,70-73] or beneficial effects. [39,71,74] PHTS data of over 3,000 children showed no correlation between donor inotrope exposure on recipient 1 year survival, even when differentiated by high verses low dose or when combined with need for cardiopulmonary resuscitation, head trauma as cause of death and prolonged ischemic time; further, donor exposure to hormonal therapy was associated with improved recipient outcomes. [50] A large single center study of 192 pediatric recipient/ donor pairs evaluating donor exposure to high dose (>5 mcg/kg/min), low dose, and no dopamine demonstrated no difference in 1-year survival and a significantly decreased incidence of post-transplant right heart failure when donors received dopamine. [71] Several adult studies have also demonstrated inotropic support to be associated with either higher[74] or similar[36] 3 year graft survival and without difference in primary graft failure. [72-74]

A particular challenge is use of donor hearts with previously depressed left ventricular function receiving inotropic support. These characteristics comprise the most common indications for pediatric organ refusal [68,69] but over the past two decades, acceptance of such organs has increased 30% without any difference in recipient outcomes. [69] A large UNOS database study of

over 11,000 adults demonstrated no difference in primary graft failure rates, 30-day, 1-, 3- or 5-year survival between those who received donor hearts with early dysfunction (average ejection fraction 35%) requiring inotropic support to achieve normal pre-implant function or those with normal function throughout the entire pre-implant period. [39] These data suggest concerns that donor inotropic support can temporarily augment donor systolic function and misrepresent eventual recipient outcomes are unfounded.

One plausible explanation for this lack of association between recipient outcomes and donor inotrope exposure, particularly in hearts initially demonstrating left ventricular dysfunction, is the commensurate component of time after brain death. As with many acute, non-ischemic myocardial insults (i.e. myocarditis), time and supportive medical management are commonly adequate to allow complete recovery. This assertion is supported by several adult studies demonstrating longer time from declaration of brain death is associated with improved rates of primary graft failure. [39,73]

Donor Electrocardiogram

Electrocardiographic (ECG) evaluation of a potential heart donor is nearly universally provided to recipient institutions to allow an assessment of prior or ongoing myocardial ischemia, intrinsic channelopathies, accessory pathways, or pathologic hypertrophy. However, no pediatric and only a few adult studies exist to guide the clinician on donor allograft acceptance based on these findings. This process is particularly challenging as ECG changes associated with brain death, the most common indication for organ donation, are well documented to include ST segment depression and elevation, T wave inversion, U waves, QT prolongation and left ventricular hypertrophy. [13,75,76] Considering these changes are attributed to the transient autonomic storm and electrolyte abnormalities that accompany brain death, [13,75,76] their impact on long-term recipient survival is uncertain.

The largest study to address this issue examined 980 adult donor ECGs, of which 51% were noted to have one or more abnormalities defined as ectopy/arrhythmia, conduction delay, ventricular hypertrophy, chamber enlargement, pathologic Q waves, ST segment changes, or

inverted T waves. [75] Pathologic Q waves had a high specificity, though low sensitivity, for the detection of reduced left ventricular ejection fraction and regional wall motion abnormalities on echocardiogram. Atrial or ventricular ectopy and conduction delays were rare. Left ventricular hypertrophy (LVH), considered a relative contraindication to heart transplantation in adult literature[77,78] due to a perceived risk of primary graft dysfunction, particularly when paired with prolonged donor ischemic times, [79] was present in 8%.[75] This was significantly more common in donors who died of cerebrovascular causes as compared to traumatic brain injury or anoxia and was hypothesized to be secondary to myocardial edema. Corrected QT (QTc) was >480 ms in 21% and >500 ms, in 15%. Although no analyses were performed regarding recipient outcomes, aside from PR and QRS intervals there were no associations between ECG findings and organ utilization.

Another adult study evaluated the association of donor QTc >500 ms on 1 year post transplant recipient outcomes. [76] At study conclusion, donor QTc prolongation was not associated with recipient survival or persistence of QTc prolongation. Of interest, however, was a significant association between donor QTc prolongation and increased risk of cardiac allograft vasculopathy which was hypothesized to be related to proinflammatory cytokines released at the time of brain death.

Given brain death's transient effect on the myocardium, it is be reasonable to repeat an ECG after periods of hemodynamic stability[75], particularly when initial studies are significantly abnormal. With the available literature to date, there is little additional guidance offered from the ECG outside of an echocardiogram, as no independent ECG components have found to be predictive of graft outcomes. [13,36,75,76] This must, however, be interpreted in the context of a known cause of death. Given that cerebrovascular causes of death result in similar abnormal ECG findings, the donor cause of death needs to be clarified to help rule out intrinsic conduction abnormalities, such as a channelopathy. [13]

Donor Echocardiographic Evaluation

All donor information provided to potential pediatric recipient institutions is intended to allow an estimate of that heart's short and long-term functional longevity. Cause of death and need for CPR describe prior finite events associated with exacerbations of catecholamine, cytokine and sympathetic nervous system up-regulation. Serum biomarkers of myocardial injury measure the immediate quantity of cellular injury associated with these prior events and their downward trend describes the time-course of insult cessation. Need for donor inotrope therapy is commonly required to offset the neurohormonal void that develops following brainstem herniation and ECG changes are typically reflective of myocardial strain and electrolyte disarray. Donor ischemia time is a predictable parameter largely determined by donor and recipient locations. Echocardiographic evaluation, however, is arguably the most representative measure of current donor left ventricular function and potentially the most important data available any potential recipient institution.

Numerous studies have demonstrated decreased utilization of potential donor hearts with echocardiographic evidence of ejection fractions less than 50%[6,17,19,68,69,80] and ISHLT guidelines have similarly recommended refusal of donor hearts with ejection fractions less than 40%.[81] This practice has been supported by several pediatric[16,17] and adult[82] studies suggesting higher rates of graft failure following transplant of hearts with ejection fractions less than 50% and a recent pediatric donor utility survey demonstrating half of all respondents would decline an otherwise acceptable organ with an ejection fraction less than 50%.[29]

Conversely, a larger number of pediatric and adult studies have demonstrated comparable recipient outcomes following transplantation of hearts with ejection fractions less than 50%[19,36,39,69,83] and/ or with evidence of segmental wall motion abnormalities. [36,83] This difference may be secondary to increased time intervals between initial echocardiograms demonstrating poor function (oftentimes shortly after herniation) and pre-harvest myocardial function, (whether documented by echocardiogram or not) with the time interval allowing for myocardial recovery from the neurologic death-induced 'catecholamine storm'.[8] Several pediatric[19] and adult[39,84] studies have documented the phenomenon of significantly improved function between initial and final (pre-harvest) echocardiogram following a combination of time and medical management using inotropic and/ or hormonal therapy. These data support

serial echocardiographic evaluation of potential donor hearts to assess for functional changes following the systemic response to brain death**.**

It is important to note a large number of studies in this document have demonstrated no difference in recipient/ graft outcomes following transplantation with donor hearts based on their history of CPR, [14,16,17,38,63,67] troponin elevations, [16,38,43,66,67] inotropic infusion exposure, [43,70,71] ischemia time[14,16,38,43,67] or cause of death, [8,11,16,34,66,67,70,85] have been in the setting of normal ejection fractions. This suggests that donor ejection fraction may be the most important information available to a potential recipient institution, a sentiment mirrored by others. [13]

Lastly, two pediatric studies have demonstrated concerning disparity in image interpretation between the 'local', donor site cardiologist and central laboratory evaluations of left ventricular function. [86,87] Considering the relative importance of echocardiographic measures of function in the decision to accept or decline a potential heart, it is reasonable for recipient sites to request direct visualization of echocardiographic images.

Summary

An extensive review of the available international scientific literature as of 2018 has determined that none of the following donor characteristics are independently associated with recipient outcomes: cause of death (aside possibly from cerebrovascular accident), donor troponin values, history of cardiopulmonary resuscitation, use of inotropic support, or ECG information (assuming a known cause of death in the setting of marked QTc prolongation as cannot otherwise rule out a channelopathy). It is important to note that available data do not address the additive effect of multiple variables in the same donor.

Although several studies have demonstrated comparable outcomes following heart transplantation with donor ischemic times greater than 6 hours, every effort should be made to keep this interval to less than 4 hours.

Seemingly, the single most important donor information provided a potential recipient institution is the echocardiographic measurement of ejection fraction. When normal, virtually all other donor factors become irrelevant. Use of donor hearts with ejection fraction less than

50% and/or with focal segmental wall motion abnormalities is somewhat more controversial. Such organs have comprised no more than 8% of the total donor pool in any of the adult or pediatric studies, and have been transplanted with mixed results. Based on the available data, it is reasonable to consider these marginal organs for transplantation but no strong recommendations can be made.

Combined with adult and pediatric studies showing marked differences in echocardiographic interpretations between local and core labs, these data lead to our assertion that every effort should be made to allow direct echocardiographic image evaluation by potential recipient sites.

Acknowledgements

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