Pediatric donor management to optimize donor heart utilization

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Abstract
Optimal management of pediatric cardiac donors is essential in order to maximize donor heart utilization and minimize the rate of discarded organs. This review was performed after a systematic literature review and gives a detailed overview on current practices and guidelines. The review focuses on optimal monitoring of pediatric donors, donor workup, hormonal replacement, and obliterating the adverse effects of brain death. The current evidence on catecholamine support and thyroid hormone replacement is also discussed. Recognizing and addressing this shall help in a standardized approach toward donor management and optimal utilization of pediatric heart donors organs.
1 | INTRODUCTION

Optimal donor management is essential in the period preceding organ procurement to maximize the function of transplanted organs and survival benefit for organ transplant recipients. Here, we present strategies for the management of deceased pediatric organ donors prior to organ procurement, with the goal to optimize donor heart utilization.

2 | METHODS

A systematic review of the literature from the Medline database was performed in November 2018 using the MeSH terms MeSH terms “Tissue and Organ Procurement,” “Donor Selection,” “Tissue and Organ Harvesting” in combination with the search term “heart,” or using one of the following search terms: “donor management,” “high-risk donor,” “marginal donor,” “donor assessment,” “donor optimization,” “DCD—donation after circulatory death,” “donor management goals,” and “expanded criteria donor” each combined with the search term “heart.” Results were narrowed with the following filters: “Language: English,” “Species: Human,” “Publication: Last 10 years,” “Age: birth—18 years.” After excluding duplicates, a total of 439 publications matching the MeSH terms were identified. Publications were then screened by authors for relevance to the present publications. A total of 105 publications were matched MeSH criteria and were rated relevant to the present paper. These publications build the basis for this review.

3 | GENERAL CONSIDERATIONS

The management of pediatric donors primarily focuses on therapeutic and supportive measures to mitigate the pathophysiological responses to brain death. The spectrum of systemic clinical sequelae of brain death ranges from minimal to severe dysautonomia and inflammatory responses. ICU management should be organized around the principles included below, with targeted strategies to stabilize hemodynamics and improve severe electrolyte derangements, thereby optimizing the viability and function of potential donor organs. In addition, cardiac-specific evaluation of the deceased potential donor during this period facilitates transplant center decision-making for donor heart selection and matching to potential recipients.

4 | GENERAL DONOR WORKUP

General donor workup includes a complete medical history and cause of death, with special emphasis on conditions that might disqualify potential donors (e.g., certain malignancies, risk factors for sudden cardiac death/malignant arrhythmias, structural heart disease, infections). In potential cardiac donors, chest radiography, ECG, and an echocardiogram for structural and functional abnormalities are indicated. Although uncommon in pediatric cardiac donors, selective imaging of the coronary arteries may be indicated to exclude coronary artery disease or congenital coronary abnormalities (e.g., Williams-Beuren Syndrome or anomalous origin of a coronary artery).

5 | DONOR MONITORING

A dedicated team in an ICU setting should manage the pediatric cardiac donor to maximize the probability of successful transplantation. Invasive monitoring is necessary for hemodynamic optimization and tailoring of medical therapy. Typical monitoring of pediatric cardiac donors should include:

- Continuous monitoring of blood pressure, heart rate and rhythm, oxygen saturation, and urine output.
- Regular laboratory monitoring including renal and hepatic function, electrolytes, serum lactate, acid-base status, and infectious parameters if clinically indicated.
- Central venous access to monitor saturation and pressure and administer medications
- Standardized echocardiographic examinations should be performed to evaluate the donor heart. Repeated echocardiograms may be required if the donor organ systolic function is impaired to assess for recovery of function or in response to changes in donor clinical condition.

6 | HEMODYNAMIC MANAGEMENT—GENERAL CONSIDERATIONS

Brain stem death is associated with a severe autonomic and inflammatory response that results in early catecholamine release (the “autonomic” or “catecholamine storm”) and later hypotension due to cardiac dysfunction and/or vasoplegia associated with inflammatory activation and loss of vascular tone. Hypovolemia may further confound cardiovascular management in the severely brain-injured patient with vigorous diuresis and diabetes insipidus. The occurrence of circulatory shock in patients following brain death is thus the consequence of complex pathophysiological interactions that impact all determinants of cardiac output (preload, contractility, and afterload). Hemodynamic management to compensate for these derangements typically includes a combination of volume resuscitation, inotropic and/or vasopressor administration, and hormonal replacement. Etiology of hypertension is usually straightforward to discern, but the pathophysiological processes contributing to donor hypotension demand thorough assessment in order to determine appropriate management—repletion of intravascular volume for hypovolemia, inotropic support for myocardial dysfunction, vasopressor, and consideration of steroid and thyroid hormone supplementation for vasoplegia.
Clinical management of the potential organ donor should aim to achieve hemodynamic stability with adequate end-organ perfusion, electrolyte balance, and urine output. Early and targeted management of the potential donor can increase the number of available donor hearts without deleterious effect on post-transplant outcomes. Importantly, the heart has potential to recover from the insults associated with brain stem death, with adequate donor resuscitation, stabilization, and time. Duration of donor optimization after brain death has implications for organ retrieval. A number of studies demonstrate improved organ donation rates after longer period of donor stabilization, in one study comparing different time points of organ donation after brain death, only 20% of donors had hearts suitable for transplantation within 24 hours of brain death, which increased to more than 50% after 36 hours. Further, a recent study of an adult cohort who received heart transplantation with donor organs with improving left ventricular systolic function demonstrated no difference in short- or long-term outcomes. These findings support optimization of clinical care of the brain dead organ donor over the first 24-36 hours in order to achieve the best status for potential organ donation. Other studies have found an increased risk of cardiac arrest in the brain dead organ donor after 30 hours; therefore, optimal timing must be chosen with care.

Specific considerations of organ donor management may depend on the mode of death. Trauma patients may require aggressive resuscitation, and reversal of disseminated coagulopathy may be necessary. History of cerebral vascular accident is associated with an acute increase in intracerebral pressure and subsequent catecholamine surge with potential for myocardial injury. History of donor CPR has been reported in 6.6%-33% of pediatric heart transplants. The management of CPR-positive donors should focus on the restoration of normal cardiac function and time for the myocardium to recover. Longer donor management times greater than 20 hours have been shown to yield increased organ procurement rates.

### 6.1 Volume replacement and choice of fluid and electrolyte replacement

Hypovolemia is often associated with brain death, so initial hemodynamic management includes intravascular volume repletion targeting euvoeemia. Monitoring of CVP, markers of end-organ function including urine output, and echocardiography reflect the adequacy of volume replacement. Failure to manage hypotension with adequate volume replacement may lead to excessive use of vasopressors, with deleterious effects on donor organs including increased myocardial oxygen consumption. There is no evidence to guide optimal choice for fluid replacement, but guidelines support volume replacement with isotonic crystalloids as first-line therapy and careful fluid selection to normalize electrolytes. To avoid decreased colloid osmotic pressure, albumin may be used to supplement crystalloid volume replacement if needed. While rarely utilized in pediatric intensive care environments, hydroxyethyl starch solutions have been associated with impaired kidney function and renal graft dysfunction in recipients and should be avoided in the management of the potential organ donor. There are no recommendations regard optimal hemoglobin levels in the potential organ donor, but in critically ill children, packed red blood cell transfusion is not recommended when the hemoglobin level is greater than 7 mg/dL. In patients with diabetes insipidus (see also hormonal replacement), serum sodium should be maintained < 150 mEq/dL. However, evidence regarding serum sodium is conflicting and recent reports challenge the importance of serum sodium in donor heart selection.

### 6.2 Vasopressor and inotropic therapy

Historically, impaired myocardial function as assessed by echocardiogram (reduced ejection fraction) and/or the use of high-dose inotropes or vasopressors, or multiple inotropes have been considered contraindications for cardiac donation or acceptance of an offered organ. In many recent studies, however, no difference in clinical outcomes was found associated with inotrope use. While the use of 2 inotropic agents and/or EF < 50% has been reported as "marginal donor" organs, multiple pediatric studies demonstrate no difference in recipient outcome when comparing these "marginal" donors to others. A review of the UNOS database revealed that even moderately depressed LV function of the donor graft was not associated with any significant difference in survival in the recipients. Increasingly, the use of vasopressors and inotropes is not considered contraindications to organ donation. In the clinical management of the organ donor, initiation of vasopressor and inotropic support should be titrated to achieve the goals of adequate CVP, normal blood pressure for age, normal urine output, and markers of adequate tissue oxygen delivery. There are no pediatric studies to inform the choice of inotropic agent or timing of initiation of vasopressor. In pediatric donors, transesophageal echocardiography should precede the initiation of vasopressor and inotropic support to inform the initial choice of vasoactive agent. In the setting of left ventricular dysfunction, an inotropic agent, according to institutional protocols, would be appropriate. If persistent hypotension reflects low SVR from vasoplegia with normal biventricular systolic function, norepinephrine or vasopressin may be commenced. No comparative data exist with regard to choice of optimal vasopressor; however, in adult studies of cardiac donation, vasopressin use in the donor was associated with increased recipient survival at 12 months, but norepinephrine use in donor was associated with reduced 1-year survival of heart recipients. Serial echocardiography should be performed to document improving left ventricular systolic function, as recovery from the event leading to brain death and the brain death process itself is well documented.
6.3 | Hormonal therapy

Endocrine abnormalities and metabolic dysfunction are associated with brain death. These changes might affect graft survival and promote hemodynamic instability as well as cardiac function. The majority of donors have significantly reduced to non-detectable levels of circulating arginine vasopressin and variable deficiencies in corticosteroids and thyroid hormones. Hormonal replacement with vasopressin, thyroid hormone, or glucocorticoids may mitigate endocrine abnormalities. There is no consensus whether hormonal replacement therapy should be prophylactically indicated or only in those donors with significant hemodynamic and electrolyte derangement. There are some adult clinical studies to suggest that hormonal resuscitation therapy is associated with increased organ recovery; however, its effectiveness has also been questioned.

In pediatrics, a registry study noted hormonal replacement therapy (defined as thyroid hormone, vasopressin, and/or glucagon) was associated with improved recipient survival.

6.4 | Vasopressin and desmopressin substitution

Up to 80% of donors have significantly reduced circulating levels of arginine vasopressin resulting from the compression of the pituitary gland during brain herniation. Depending on the remaining levels of arginine vasopressin, donors develop diabetes insipidus, which is characterized by inappropriate urine output, hypotension, hypernatremia, and hyperosmolarity. Whether arginine vasopressin or desmopressin should be used for hormonal replacement depends on the donors’ clinical presentation. Arginine vasopressin is typically administered in donors with neurogenic hypotension refractory to adequate fluid resuscitation and without evident signs of diabetes insipidus. Desmopressin has a stronger antidiuretic effect as compared to arginine vasopressin. The vasoconstrictive effect of desmopressin, however, is negligible. Therefore, desmopressin is the substitute of choice in patients with diabetes insipidus without neurogenic hypotension. Desmopressin is primarily used to control urine output and normalize serum sodium levels.

6.5 | Thyroid hormone substitution

Several preclinical studies have demonstrated a significant decline of T3 and T4 after brain death. However, these findings are only in part reproducible in humans. It has also been demonstrated that a decline of T3 and T4 is associated with depletion of myocardial energy stores, myocardial dysfunction, and development of an anaerobic metabolic state. Administration of thyroid hormones can reverse these pathological findings, improve cardiac function, and reverse the anaerobic metabolic state. Clinical studies in adults, however, are conflicting, and both large meta-analysis and prospective randomized studies failed to establish a beneficial effect of thyroid hormone therapy. Guidelines currently recommend the administration of thyroid hormones, with either T3 or T4, in patients with reduced myocardial function and therapy-resistant hemodynamic instability.

6.6 | Glucocorticoid substitution

Adrenal dysfunction is frequent after brain death. Glucocorticoid substitution is performed by many centers to augment steroid hormone production and for its anti-inflammatory effect. In addition, methylprednisolone is often used in the setting of high vasoressor support to stabilize hemodynamics despite only few supportive data. The clinical benefit of glucocorticoid substitution in pediatric patients remains to be proven.

6.7 | Retrieval issues

IT has been one of the main parameters of concern in donor organ acceptance and utilization with the goal being to minimize it as much as feasible.

One alternative to decrease cold IT is normothermic donor heart perfusion, which can reduce total IT for conventional donor organ preservation. Normothermic donor heart perfusion allows for extended out of body time up to 8 hours, expanding potential geographic zones for organ procurement and reducing the detrimental effects of the cold ischemic storage. The PROCEED trial utilized the Organ Care System for normothermic donor heart perfusion. Thirty-eight patients were enrolled and showed no statistically significant difference in 2-year patient survival rate in patients with normothermic donor heart perfusion or cold IT, no difference in freedom from non-fatal major cardiac events or cardiac allograft vasculopathy. Secondary outcomes focusing on allograft rejection rates also demonstrated comparable results. The use of normothermic organ procurement is increasing in adults both to increase the use of marginal donor hearts, to allow for more distant procurement, and (perhaps most importantly) to increase the potential for DCD donors. As it becomes more standard for use in adults, it may become feasible for donor recoveries performed for larger children. It is not clear whether a device sized appropriately for smaller children will become available.

A review by Latchan et al provides information on the biochemical comparison of common preservation solutions and relevant preservation studies, and this notably makes recommendation for the use of UW solution in cardiac preservation. Hypothermia alone is unable to abolish all cellular damage as metabolism persists at approximately 5%-10% of normal. In addition, hypothermia can lead to Na/K ATPase alterations, ATP depletion, dysregulation of Ca homeostasis, mitochondrial perturbations, xanthine oxidase accumulation, and increase levels of ROS, which may have deleterious effects on cellular viability.

Many new ideas based upon experimental data have been postulated but still have to find their way to the clinical setting. It is
notable that no major changes have been introduced in the technique of heart preservation over the recent years and outcomes are dependent on a range of factors.

6.8 | Summary statement

Pediatric donor management focuses on therapeutic and supportive measures to counteract the pathophysiological response to brain death. In addition, donor management encompasses the collection of data necessary to evaluate the suitability of cardiac donors. A combination of volume replacement, vasopressor, and inotropic support as well as hormonal replacement are necessary to stabilize donor hemodynamics and preserve organ function prior to organ retrieval.

AUTHORS’ CONTRIBUTIONS

Daniel Zimpfer, Peta M. A. Alexander, Ryan R. Davies, Anne I. Dipchand, Brian Feingold, Anna Joong, Karen Lord, Richard Kirk, Angie Scales, Renata Shih, and Oliver Miera involved in the literature review, writing, and revision of manuscript.

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