

BRIEF REPORT

Pediatric Heart Transplantation after Declaration of Cardiocirculatory Death

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SUMMARY

In three infants awaiting orthotopic cardiac transplantation, transplantation was successfully performed with the use of organs from donors who had died from cardiocirculatory causes. The three recipients had blood group O and were in the highest-risk waiting-list category. The mean age of donors was 3.7 days, and the mean time to death after withdrawal from life support was 18.3 minutes. The 6-month survival rate was 100% for the 3 transplant recipients and 84% for 17 control infants who received transplants procured through standard organ donation. The mean number of rejection episodes among the three infants during the first 6 months after surgery was 0.3 per patient, as compared with 0.4 per patient among the controls. Echocardiographic measures of ventricular size and function at 6 months were similar among the three infants and the controls (left ventricular shortening fraction, 43.6% and 44.9%, respectively; $P=0.73$). No late deaths (within 3.5 years) have occurred in the three infants, and they have had functional and immunologic outcomes similar to those of controls. Mortality while awaiting a transplant is an order of magnitude higher in infants than in adults, and donors who died from cardiocirculatory causes offer an opportunity to decrease this waiting-list mortality.

PEDIATRIC HEART TRANSPLANTATION AFTER THE DECLARATION OF BRAIN death in donors has been performed for more than 25 years in more than 6000 recipients.¹ The first successful heart-transplant procedure in an infant was reported 20 years ago, and decades-long survival has been reported.^{1,2} The average survival for children who are alive 1 year after transplantation is more than 15 years and exceeds that of adults.³ However, the risk of death while awaiting a donor is highest for children awaiting a cardiac transplant.⁴ Infant heart-transplant recipients face up to a 25% waiting-list mortality, which is an order of magnitude higher than that of adult heart-transplant recipients.^{4,5} Mechanical circulatory support, which can be crucial for many adult heart-transplant recipients, is generally unavailable for infants.

Organ donation after death from cardiocirculatory causes has been increasingly used for kidney, liver, and even lung transplantation.⁶ The first successful heart transplantation in an adult involved a donor who died from cardiocirculatory causes,⁷ but concerns about the vulnerability of the heart to ischemic injury has limited further transplantation in adults of hearts from donors who died from cardiocirculatory causes. To our knowledge, there have been no previous reports of transplantation in children of hearts from donors who died from cardiocirculatory causes.

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However, pediatric heart transplantation has been performed after prolonged ischemic injury in a donor, including in children who have died from the sudden infant death syndrome, and the results were similar to those for donors without ischemic cardiac injury.^{1,8} On the basis of experiments in animals, heart transplantation involving donors who died from cardiocirculatory causes can be performed successfully.⁹

End-of-life care is an important part of the family-centered environment in pediatric care facilities, and families of dying children overwhelmingly support organ donation. In the typical children's hospital, on any given day, there are between 2.2 and 10.6 children who will die in the hospital, and approximately half of these children were receiving ventilator support and were hospitalized for a mean of 16 days before death.¹⁰ A survey at a leading children's hospital reported that 35% of deaths followed withdrawal of life support, and transplants from donors who died from cardiocirculatory causes would have been the only possible route to organ donation available to the family.¹¹ According to the same survey, 75% of patients died within 30 minutes after the withdrawal of life support. Thus, a child's death can be anticipated and considered within a family-centered end-of-life care plan, which can include the possibility of donation after withdrawal of life support and subsequent circulatory or cardiac death.

We report on an institutional clinical trial of heart transplantation involving three infants who underwent orthotopic transplantation of hearts from donors who died from cardiocirculatory causes. The recipients were followed for a minimum of 6 months after surgery, while receiving standard immunosuppression therapy and undergoing surveillance for rejection episodes.

METHODS

The transplantations were performed between May 2004 and May 2007 at the Denver Children's Hospital. Written informed consent was obtained from the parents of the recipient infants as part of the protocol, which was approved by the institutional review board and the hospital ethics committee. Families of all infants (<18 months old) who were potential transplant recipients (with United Network for Organ Sharing [UNOS] status 1A) were given the options of consenting to receive an or-

gan from a donor who died from cardiocirculatory causes or from a donor after the declaration of brain death.

Physicians not involved in the care of recipients made the medical decision to withdraw life support in potential donors, with the consent of their families, on the basis of the futility of ongoing care and the requirement for life support to maintain viability; the decision was made independently of considerations of organ donation. Families of potential donors who were predicted to die from cardiocirculatory causes were then referred to the organ-procurement organization. If the organization had a local potential recipient of a compatible blood group awaiting heart transplantation and with the highest UNOS status (1A), the family was given the option of organ donation from a donor who died from cardiocirculatory causes. In addition to the three donors described here, nine other potential donors underwent withdrawal from life support and died during the study but could not donate because there was no suitable recipient. Written informed consent for donation, as well as for the use of heparin and invasive central catheters, was obtained from the parents or guardians of patients who died from cardiocirculatory causes by the organ-procurement organization.

ORGAN-DONATION PROTOCOL

Donor care was provided under the direction of the intensive care team. Withdrawal of life-supporting ventilation was performed in the operating room by the intensivist and the primary nurse. On one occasion, the family chose to be with their child during withdrawal of life support. Each patient was prepared for surgery and monitored with the use of electrocardiography and pulse oximetry. Femoral venous and arterial sheaths were placed with the use of local anesthesia, and an initial heparin bolus of 100 U per kilogram of body weight was given intravenously. Comfort care was given by the intensive care team and included sedation and analgesia typical for withdrawal of life support: fentanyl at a mean dose of 4 μ g per kilogram and lorazepam at a mean dose of 0.1 mg per kilogram. Extubation was performed, followed by an additional intravenous dose of 300 U of heparin per kilogram. The attending physician in the critical care unit monitored the patient for evidence of cardiocirculatory function by means of auscultation and observation for arterial pulsation.

When cardiocirculatory function ceased, the first patient was observed for 3 minutes before death was declared and the organ-donation process initiated. On the basis of recommendations of the ethics committee, for the other two donors, the observation period was shortened to 1.25 minutes.

If death occurred within 30 minutes after extubation, the patient was considered to be a candidate for donation, and cold preservation fluid (30 to 50 ml per kilogram) was infused through the distal port of a balloon arterial catheter placed in the ascending aorta. At the same time, a median sternotomy was performed, and topical cooling was begun. The inferior vena cava was immediately opened. In the second and third donors, venous-blood withdrawal was performed simultaneously with aortic infusion to prevent cardiac distention. After organ donation, the family of the donor was offered the choice of spending time with their child.

TRANSPLANTATION AND FOLLOW-UP

Transplantation was performed with the use of standard techniques, and routine immunosuppression therapy was started. Rejection surveillance was performed according to clinical and echocardiographic criteria. Troponin I levels were measured before extubation of the donor and 12 hours after transplantation.

STATISTICAL ANALYSIS

Both the data and safety monitoring board and the hospital ethics committee reviewed the outcome for each transplant recipient. The primary end point was death within 6 months after transplantation. Secondary end points were waiting time

to transplantation, systolic function at 6 months (as determined on echocardiography), and occurrence of a rejection episode within 6 months. The continuous variables were compared between the three recipients and control infants with the use of a two-sided t-test. P values less than 0.05 were considered to indicate statistical significance.

RESULTS

TRANSPLANTATION

Orthotopic heart transplantation involving donors who died from cardiocirculatory causes was performed in three recipients at a mean age of 2.2 months. The diagnosis leading to transplantation was complex congenital heart disease in two patients (one with a double-outlet right ventricle, transposition of the great vessels, a ventricular septal defect, and coarctation and the other with a hypoplastic left ventricle, mitral stenosis, aortic stenosis, and severely restricted atrial-septal communication) and, in the third patient, severe dilated cardiomyopathy requiring continuous intravenous inotropic support. Both infants with congenital heart disease had previously undergone procedures to either attempt to correct or to palliate the anatomical problem and were believed to be at an unacceptably high risk for further interventions. The first recipient had undergone cardiac repair and was discharged home before being readmitted for cardiovascular collapse associated with coronary artery occlusion and left ventricular infarction. Extracorporeal membrane oxygenation was initiated before transplantation to maintain cardiac output, and he required such support for 36 hours after transplantation.

Table 1. Characteristics of Heart Transplantation Involving Three Donors Who Died from Cardiocirculatory Causes.*

Donor	Time to Death after Withdrawal of Life Support	Total Ischemic Time	Troponin I Level		Recipient Outcome at 6 Mo
			Before Withdrawal of Life Support (in Donor)	After Transplantation (in Recipient)	
	<i>min</i>			<i>ng/ml</i>	
1	11.5	221	0.2	30	Alive
2	27.5	127	0.5	23	Alive
3	16.0	139	0.3	127	Alive
All	18.3±8.3	162±51	0.3±0.2	60±58	

* Plus-minus values are means ±SD.

After explantation of the donor's heart, the mean cold ischemic time was 106 minutes and the mean total ischemic time (to aortic cross-clamp removal in the recipient) was 162 minutes (Table 1). The mean troponin I level at 12 hours after surgery was 60 ng per milliliter. The postoperative course and amount of inotropic support did not differ from those of traditional donors. The mean length of hospital stay after transplantation was 20 days, similar to that among traditional transplant recipients.

Heart transplantation was performed in 17 infants less than 18 months old (mean age, 3.0 months), with the use of traditional donation after brain death, at Denver Children's Hospital during the same period. The 6-month survival rate was 100% among the 3 recipients of transplants from donors who died from cardiocirculatory causes and 84% among the 17 recipients of transplants from traditional donors. Coronary artery disease has not developed in any of the patients whose donors died from cardiocirculatory causes.

CARE OF DONORS

All the donors who died from cardiocirculatory causes were born at other hospitals and were transferred for neonatal critical care. They underwent continuous bedside amplitude-integrated electroencephalography and daily neurologic examinations, which revealed severe neurologic injury. A complete 16-lead electroencephalogram and a separate, formal neurologic consultation were obtained, confirming the injury and the poor prognosis, before the decision was made to withdraw life support. Organ donation followed release by the coroner. The mean time to declaration of death was 18.3 minutes (range, 11.5 to 27.5) (Table 1). The cause of death of all three donors was birth asphyxia; in one, the asphyxia was precipitated by placental rupture. The mean age at donation was 3.7 days, and the mean weight at donation was 3.2 kg. The mean troponin I level before withdrawal of life support was 0.33 ng per milliliter (normal level, <0.10). All families of donors who died from cardiocirculatory causes chose to meet only with the critical care staff and staff of the organ-procurement organization after donation. The families reported no adverse experiences associated with this family-centered approach to end-of-life care and organ donation.

FOLLOW-UP

All three heart-transplant recipients survived to 6 months. The mean number of rejection episodes was 0.3 per patient, which was not significantly different from the rate of 0.4 episode when standard organ donation was used. Echocardiographic measures of cardiac function were similar between the three recipients and the controls. The mean (\pm SD) left ventricular shortening fraction during systole at 6 months was $43.6\pm 3.4\%$ among the three patients who received transplants from donors who died from cardiocirculatory causes and $44.9\pm 6.6\%$ among controls ($P=0.73$). The left ventricular end-diastolic volume (expressed as the percent of the predicted normal value) was $72.6\pm 13\%$ among the three recipients and $81.9\pm 16\%$ among controls ($P=0.36$).

DISCUSSION

Children, and infants in particular, have the greatest risk of death while awaiting orthotopic heart transplantation. In addition, increased waiting time before transplantation adversely affects late neurologic development.¹² Many children die in children's hospitals each day after withdrawal of futile care. Thus, we developed this clinical trial of the feasibility of pediatric heart transplantation involving donors who died from cardiocirculatory causes. Before the trial was begun, an extensive period of education, discussion, and preparation was undertaken within our hospital and in programs already using donors who died from cardiocirculatory causes. After each transplantation involving these donors, there was extensive institutional debriefing and review by the ethics committee and the data and safety monitoring board.

The outcomes after transplantation of hearts from donors who died from cardiocirculatory causes were similar to those associated with traditional organ donation. All three recipients survived despite being at high risk for death, with excellent late heart function and no evidence of increased immunologic risk. The small number of patients involved limits the conclusions that can be drawn beyond proof of principle. Still, the potential effect is large. During the 3-year period of this trial, a total of 12 potential donors who died from cardiocirculatory causes were identified,

which could represent a 70% increase in organ donation (based on the total number of transplantations in infants at Denver Children's Hospital) and confirms previous estimates.¹¹ However, during this same 3-year period, only one pediatric heart donor who was declared brain-dead and no newborn heart donors defined by traditional criteria were identified within Denver Children's Hospital. Thus, even just the three transplants from donors who died from cardiocirculatory causes represent a 300% increase in the rate of local donation.

The donation protocol we used for patients who died from cardiocirculatory causes was successful, but some features may not be required. The mean time to death was 18 minutes, less than the maximum of 30 minutes according to the protocol. The analgesia regimen given as comfort care at the time of withdrawal from life support actually involved lower doses than would have been given to similar infants who could not be considered for organ donation. The dose of heparin has not been critically evaluated but is within the range used for cardiopulmonary bypass. The importance of cold perfusion of the ascending aorta has been shown in experiments¹³ but has not been critically evaluated in this or other clinical trials. The appropriate period of observation after the cessation of cardiocirculatory function and before the declaration of death has not been established. We initially used a 3-minute period after loss of cardiac function. This time was based on a recommendation of 2 minutes in the critical care literature.¹⁴ After the first donation, the ethics committee recommended a period of observation of 1.25 minutes to reduce the risk of injury from warm ischemia. This recommendation was based on the longest reported period before autoresuscitation of a child or adult, 60 seconds. The subsequent two donations were performed after an observation period of 1.25 minutes after the loss of cardiocirculatory function. The postoperative and immunosuppressive care followed our standard protocol for traditional donors. The absence of previous pediatric experience and the small number of patients reported on here precludes recommendations of the limit of warm ischemia time or unique care that could apply to pediatric heart donors who died from cardiocirculatory causes and the subsequent recipients.

The first recipient required extracorporeal membrane oxygenation after transplantation, but this

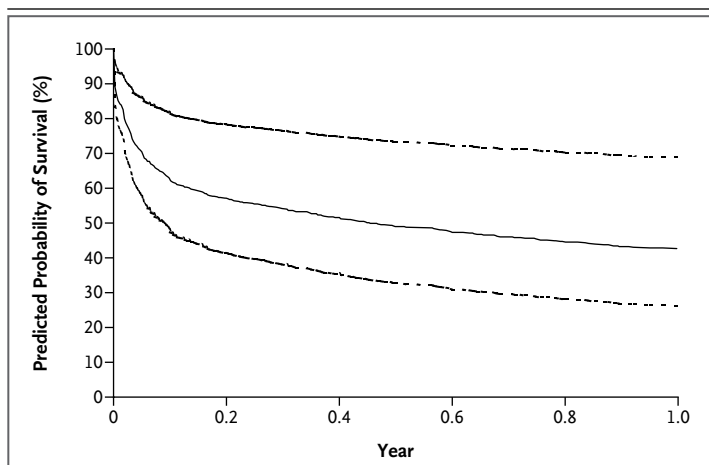


Figure 1. Predicted Probability of Survival of the First Recipient.

The probability of survival was based on International Society for Heart and Lung Transplantation risk factors of the donor and recipient at the time of transplantation, assuming donation from a patient after brain death. This recipient was a 2-month-old boy who had congenital heart disease diagnosed at birth, weighed 4.1 kg, had a creatinine level of 1.5 mg per deciliter (133 mmol per liter), and was receiving extracorporeal membrane oxygenation and ventilator support. The donor was a 3-day-old boy weighing 2.8 kg. The upper and lower curves indicate the 95% confidence interval.

requirement was not surprising, because the surgery was high risk: the patient was critically ill despite extracorporeal membrane oxygenation before transplantation, and the donor:recipient weight ratio was 0.7 (Fig. 1). This trial does not allow us to answer the question of how long warm ischemia can be tolerated and still permit recovery of heart function. The experience with these three high-risk patients supports the concept that the heart, like other solid organs, is capable of functioning adequately in a physiologically viable recipient after transplantation, despite cardiocirculatory death in the donor. Perhaps the previous ischemic injury in the donor, as evidenced by the increased troponin I level before donation, confers some ischemic preconditioning that makes recovery more likely.¹⁵

Donors who died from cardiocirculatory causes offer an opportunity to reduce waiting time and waiting-list mortality among children whose survival depends on a heart transplant. This study was performed in the context of a large pediatric transplant program, yet most potential donors who underwent withdrawal from life support could not be considered, because there was no compatible local recipient. The majority of pediatric donor hearts are shared among transplan-

tation regions. For pediatric heart donation and transplantation involving patients who die from cardiocirculatory causes to become a more frequent option for end-of-life care and to affect significantly the nationwide risk of dying while waiting, the concept of distant sharing of donated organs from these donors should be considered.

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APPENDIX

Members of the Denver Children's Hospital Pediatric Heart Transplant Team were as follows: M.M. Boucek, B. Pietra, S. Miyamoto, D. Campbell, M. Mitchell, C. Mashburn, D. Gilbert, A. Ballard, C. Connell, D. Ripe, B. Diamond, F. Legette, S. Anderson.

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