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Outcome of Extracorporeal Membrane Oxygenation for Early Primary Graft Failure After Pediatric Heart Transplantation

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Objectives We sought to analyze the indications and outcome of extracorporeal membrane oxygenation (ECMO) for early primary graft failure and determine its impact on long-term graft function and rejection risk.

Background Early post-operative graft failure requiring ECMO can complicate heart transplantation.

Methods A retrospective review of all children requiring ECMO in the early period after transplantation from 1990 to 2007 was undertaken.

Results Twenty-eight (9%) of 310 children who underwent transplantation for cardiomyopathy (n = 5) or congenital heart disease (n = 23) required ECMO support. The total ischemic time was significantly longer for ECMO-rescued recipients compared with our overall transplantation population (276 ± 86 min vs. 242 ± 70 min, $p < 0.01$). The indication for transplantation, for ECMO support, and the timing of cannulation had no impact on survival. Hyperacute rejection was uncommon. Fifteen children were successfully weaned off ECMO and discharged alive (54%). Mean duration of ECMO was 2.8 days for survivors (median 3 days) compared with 4.8 days for non-survivors (median 5 days). There was 100% 3-year survival in the ECMO survivor group, with 13 patients (46%) currently alive at a mean follow-up of 8.1 ± 3.8 years. The graft function was preserved (shortening fraction 36 ± 7%), despite an increased number of early rejection episodes (1.7 ± 1.6 vs. 0.7 ± 1.3, overall transplant population, $p < 0.05$) and hemodynamically comprising rejection episodes (1.3 ± 1.9 vs. 0.7 ± 1.3, overall transplant population, $p < 0.05$).

Conclusions Overall survival was 54%, with all patients surviving to at least 3 years after undergoing transplantation. None of the children requiring >4 days of ECMO support survived. Despite an increased number of early and hemodynamically compromising rejections, the long-term graft function is similar to our overall transplantation population. (J Am Coll Cardiol 2009;54:730–7) © 2009 by the American College of Cardiology Foundation

Heart transplantation in children with end-stage heart failure secondary to cardiomyopathy or failed palliation of congenital heart disease (CHD) is a good option with improving outcomes (1). One of the most common complications in the immediate period after transplantation is early graft failure. Graft failure can result from long ischemic time, inadequate myocardial preservation at time of procurement, hyperacute rejection, or poor adaptation of the graft to the recipient's hemodynamic environment (2). Either as a consequence of left heart failure or as a result of single ventricle physiology, pulmonary vascular resistance (PVR) in many pediatric recipients is increased, resulting in the risk of right ventricular failure after transplantation.

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Measures aimed at decreasing PVR after transplantation include the use of inhaled nitric oxide as well as medications with pulmonary vasodilator effects, such as prostacyclin, isoproterenol, and milrinone (3). Graft ventricular function is also commonly supported post-operatively with inotropes (e.g., dopamine, dobutamine, low-dose epinephrine, or milrinone). However, despite these interventions, ventricular failure may persist, and mechanical circulatory support becomes necessary. Extracorporeal membrane oxygenation (ECMO) is widely used for post-cardiotomy low cardiac output syndrome (LCOS) in children and is occasionally

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required after pediatric heart transplantation (4–6). The objectives of this study were as follows: 1) to describe the indications and outcome of ECMO for early primary graft failure after heart transplantation in children; 2) to identify markers predictive of ECMO survival in this patient population; and 3) to determine the impact of early ECMO on long-term graft function and rejection risk.

Methods

Transplantation. We reviewed our institutional heart transplant database from 1990 to 2007. After approval by our institutional review board, all children requiring ECMO in the post-operative transplantation period were included in the study. The course after transplantation for all eligible patients was reviewed. Our institutional transplantation methodology has been previously described but will be reviewed here (7). Donor hearts are procured in standard fashion, with great vessel lengths harvested as determined by recipient anatomy. Roe's solution is used for donor cardioplegia. One of the ECMO-rescued recipients who survived underwent transplantation from a nonbeating heart donor. Organ procurement in the setting of donation after cardiac death has been previously described by our group (8). All of the other patients underwent transplantation from standard brain-dead, heart-beating donors. Moreover, there were no changes in our procurement practices throughout the duration of this study period.

Milrinone, dopamine, isoproterenol, and occasionally epinephrine are commonly used for inotropic support in the immediate post-transplantation period. Nitric oxide is systematically used in patients with an elevated PVR documented before transplantation (PVR ≥5 Wood units/m^2). Triple immunosuppression with methylprednisolone for 48 h, low-dose cyclosporine, and azathioprine is used perioperatively. Induction therapy with methylprednisolone and antithymocite globulin (Thymoglobulin, Genzyme Corp., Cambridge, Massachusetts) was used until 1998, at which time Thymoglobulin was replaced by antithymocyte globulin (American Medical Resources, Nashville, Tennessee). Low-dose cyclosporine (target level 40 to 70 ng/ml) and azathioprine were administered throughout induction. At discharge, maintenance immunosuppression consisted of cyclosporine (target level 175 to 225 ng/ml) and mycophenolate mofetil (target level 2 to 4 μg/ml) (9). In patients with an open chest or dependent on mechanical support (ECMO), induction therapy was withheld until chest closure and/or decannulation was achieved because of the increased risk of infection.

ECMO. A standardized ECMO circuit was used with appropriately sized cannulas according to the patient size (6). No other types of mechanical support devices were used during the course of this study. Transthoracic cannulation through an open chest was used in all patients via the right atrium and ascending aorta. Pump flow was regulated according to systemic perfusion, blood pressure tracing, and systemic and mixed venous oxygenation. Inotropic and ventilatory supports were weaned as tolerated during ECMO support. In patients with poor left ventricular function, venting of the left atrium or transcatheter atrial balloon septostomy was performed for left-sided decompression whenever required. Left atrial decompression was indicated in the setting of inadequate left ventricular decompression, resulting in increased left atrial pressure and/or pulmonary edema. Activated clotting time was maintained between 180 and 220 s with heparin infusion. Hemofiltration was used as required depending on the renal function and fluid status. Graft function recovery was regularly assessed by transthoracic echocardiography. Increased inotropic and ventilatory support was used for weaning off ECMO. Chest closure was usually delayed until 24 to 48 h after decannulation.

Abbreviations and Acronyms

ACT = activated clotting time
CHD = congenital heart disease
ECMO = extracorporeal membrane oxygenation
LCOS = low cardiac output syndrome
OHT = orthotopic heart transplantation
PVR = pulmonary vascular resistance
VAD = ventricular assist device

Outcome measures. Diagnosis of acute graft rejection in our institution is based on clinical presentation, echocardiographic or electrocardiographic findings, hemodynamics at time of catheterization, and/or endomyocardial biopsy evidence of rejection (10–12). Hemodynamically significant or compromising rejection is defined as a rejection episode for which the patient required intravenous inotropic support while undergoing treatment for rejection. Hyperacute graft rejection is defined as occurring during the immediate post-operative course after transplantation. Early rejection is defined as an acute graft rejection episode occurring during the first year after transplantation, and very early rejection as occurring during the first month after transplantation. Treatment of acute graft rejection includes anti–T-cell antibodies (antithymocyte globulin or OKT3) for 7 to 10 days in combination with steroids (4 doses) and the administration of intravenous immunoglobulin per institutional protocol (12). Transplant coronary artery disease is diagnosed by angiography or intravascular ultrasound and is defined as any luminal irregularities or stenosis that varied from the patient's previous angiography or intimal thickening ≥3 mm according to the Stanford classification (13,14).

Outcome was analyzed in 2 groups: 1) those successfully weaned off of ECMO and discharged alive (survivor group); versus 2) those who died while on ECMO or in the post-decannulation period (nonsurvivor group). The long-term outcome of the ECMO survivors was compared with our overall transplant population.

Statistical analysis. Data are presented as mean ± SD. When the population does not follow a normal distribution, median values are given. Intergroup comparison was conducted with an unpaired Student *t* test. Comparison of