Pediatric Cardiac Surgery Annual

Heart Transplantation in Children for End-Stage Congenital Heart Disease

Anees J. Razzouk and Leonard L. Bailey

Heart transplantation (HT) as primary therapy for children with congenital heart disease (CHD) has become unusual. With improved early results of reconstructive surgery, the population of children and adults surviving with CHD is expanding. End-stage CHD related to myocardial dysfunction or circulation failure after prior surgery is becoming more common as an indication for HT. This heterogeneous group of CHD recipients referred for HT presents unique decision-making, technical, and physiologic challenges. Historically, a diagnosis of CHD has been a major risk factor for early mortality after HT. Rescue HT, especially in the setting of failing Fontan physiology, has the worst outcome. Early referral (before end-organ damage), proper selection, and optimization of recipients, as well as meticulous intra- and postoperative management are crucial to improving early outcomes of HT in this population. Beyond the early post-HT period, children with end-stage CHD experience long-term survival comparable to most other non-CHD recipients.

Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann 17:69-76

Introduction

Improved early outcomes of reconstructive surgery has resulted in an expanding population of children and adults who are presently living with their complex congenital heart disease (CHD), many of them living quite well. Primary heart transplantation (HT) has been irrelevant to their survival beyond early infancy. So, this once nearly doomed cohort of neonates, most of whom were born with lethal CHD, is now growing up with expectations of reaching the joys and vicissitudes of adult life, and beyond. In reality, however, data suggest that not all of these youngsters are destined to achieve these ideal expectations. Some will not reach childhood, much less adulthood, without additional surgical help. Instead, 10% to 20% will reach the end-stage of their CHD related to myocardial dysfunction or circulatory failure, and they will be referred for HT.[1] They have become, and are, a heterogeneous group of potential HT recipients who present with unique decision-making, anatomic, and physiologic challenges.

Historically, a congenital diagnosis has accounted for 59% of infants < 1 year of age, 37% of children age 1 to 10 years, 23% of adolescent patients age 11 to 17 years, and 3% of adults.[2,3] HT for CHD has always been associated with worse surgical outcomes than HT for cardiomyopathy because of technical complexities and physiologic challenges of the operation. In addition, diagnosis of CHD remains a significant risk factor for 1-year and 5-year mortality after HT in both pediatric and adult recipients.[2,3] Rescue HT, especially in the setting of failing Fontan circulation, has had the worst outcomes. Early referral (before advanced end-organ damage), proper selection and optimization of recipients, and meticulous intra- and post-operative management are crucial to improving operative outcomes of HT in this population. This review will address the unique challenges of HT in patients with CHD, particularly those who have had previous repair or palliation.

Evolving Indications for HT

In recent years, the indications for HT in infants and children with CHD have changed significantly with fewer cardiac defects (e.g., complex single ventricle [SV] anomalies) requiring HT as primary therapy. HT is indicated for two-ventricle patients (e.g., tetralogy of Fallot, truncus arteriosus, Shone's complex, d- and l-TGAs, Ebstein's anomaly) with end-stage heart failure owing to severe myocardial dysfunction, irreparable valve disease, or intractable arrhythmias. However, failed

Department of Cardiovascular and Thoracic Surgery, Loma Linda University Children's Hospital, Loma Linda, CA.

Address correspondence to Anees Razzouk, MD, 11175 Campus St., Suite 21121, Loma Linda, CA 92354. E-mail: arazzouk@llu.edu

http://dx.doi.org/10.1053/j.pcsu.2014.01.009

surgical palliation is becoming the predominant indication for HT in children with CHD. Isomerisms, issues of situs, and visceral heterotaxia may add to surgical complexity but do not contraindicate HT.

Single-ventricle patients, of variable anatomic substrates and at different stages of palliation, may require HT for progressive systolic or diastolic ventricular dysfunction, irreparable atrioventricular valve regurgitation, worsening hypoxemia, elevated pulmonary vascular resistance (PVR) or arrhythmias. Patients with systemic complications of Fontan physiology represent a unique and expanding group being referred for HT. Specific indications include protein-losing enteropathy, plastic bronchitis, stroke, thromboembolism, refractory ascites, and early cirrhosis of the liver.

Potential candidates with flexible PVR ≤ 5 Wood units (wu) and/or transpulmonary gradient ≤ 10 mmHg usually have an acceptable risk for HT. Patients with PVR $>$ 9 wu and transpulmonary gradient $>$ 16 mmHg are not suitable for HT. Patients with elevated PVR (5 to 9 wu) require preoperative testing of pulmonary vasoreactivity and are at risk for early post HT graft failure. These guidelines may not necessarily apply to patients with Fontan circulation where a non-pulsatile flow state, low cardiac output, and presence of collaterals or a fenestration make the assessment of PVR impractical. In this unique circulation, PVR is often underestimated.

Absolute anatomic contraindications to HT in CHD are rare, but may include severe diffuse hypoplasia of pulmonary arteries or irreparable pulmonary venous malformations.

Combined heart–liver or heart–kidney transplants may be indicated in patients with irreversible single organ (liver or kidney) failure associated with chronic congestive heart failure.

Timing of Referral for HT

The decision for HT in patients with CHD may be simple or remarkably complex. The population is heterogeneous with variability in age, genetic substrate, support systems, structural anomalies, dysrhythmias, non-cardiac risk factors, number and complexity of previous operations, symptoms, and end-organ function. The classic timing of listing for HT for any indication has been when the expected survival at 2 years is 50%. Such timing is difficult to predict in CHD patients who may "survive" for years, albeit with limited functional reserve and marginal cardiac output. While exercise protocols, metabolic testing, and chemical markers may provide significant prognostic information, they are not necessarily reliable in predicting the need for HT. The risks and benefits of additional conventional palliation must be considered and compared with those of HT. For high-risk candidates, mechanical circulatory support as a bridge or destination therapy is evolving as a viable option.[4] The period on a HT waiting list can be long, and up to 20% of patients may die waiting, depending on their status and comorbidities.[5,6] A diminished quality of life with intermittent symptoms and frequent hospitalizations should prompt referral for HT. Early listing (before end-organ dysfunction and inotropic or ventilatory support) will reduce waiting list mortality and improve post-HT outcomes.

Pre-HT Evaluation

The complex anatomy of CHD, especially in the setting of multiple previous operations, requires detailed pre-HT imaging using echocardiography, cardiac magnetic resonance imaging, or computed tomographic angiography. Information regarding the proximity of the heart, great vessels, or conduits to the sternum, the anatomy of the systemic and pulmonary venous connections, the anatomy of the pulmonary arteries, the presence of aortic arch obstruction/coarctation, and the presence of important aorto-pulmonary collaterals is essential. Imaging may extend to the neck and groins to identify alternative sites for cannulation, and to the liver to detect cirrhosis or other liver lesions.

Cardiac catheterization and full hemodynamic evaluation is performed in all patients. Coil embolization of significant AP collaterals may be performed pre or immediately post HT to reduce the risk of high-output graft failure.

Multiple operations, with exposure to blood products and allograft patches or conduits, contribute to increased anti-HLA antibodies in patients with end-stage CHD. High levels of sensitization may increase waiting time and contribute to early graft failure and post-HT mortality. Panel reactive antibody (PRA) screening identifies sensitized patients and guides in pre- and post-HT immunomodulation therapy. Candidates with high immunologic risk (PRA $>$ 20%) receive pre HT intravenous immunoglobulin and plasmapheresis, both of which are continued postoperatively, when they also receive thymoglobulin and other immunosuppressive agents. A prospective cross-match is rarely necessary, and has been largely replaced by virtual cross-matching.

Pre-HT coagulation abnormalities are often present as a result of liver dysfunction or chronic anticoagulation for arrhythmias, Fontan circulation, mechanical valve prostheses, or thromboembolism. Correction of coagulopathy, when possible, can reduce the need for post-HT blood transfusion and will decrease respiratory and metabolic morbidity. Other preoperative challenges that should be recognized and optimized before HT include compromised nutritional state (especially in the setting of protein-losing enteropathy or ascites), chronic anemia, susceptibility to infection with asplenia or DiGeorge syndrome, chronic hypoxemic state limiting neurologic reserve, and chronic low cardiac output state causing end-organ dysfunction.

Acute or acute-on-chronic renal dysfunction is not a contraindication to HT, although its post-HT reversibility is difficult to predict. Infants and young children may require placement of a peritoneal dialysis catheter at the time of, if not before, HT. Older children and adults may require hemodialysis. Minor liver abnormalities (cholestasis, biochemical or coagulation disorders) are common in patients with chronic heart failure and are usually correctable during and after HT. However, SV patients with a Fontan circulation are at risk of developing major