Preoperative assessment and management of pediatric heart transplantation

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Abstract

The period of preoperative management of the pediatric cardiac transplant patient can be divided into three phases: determination of transplant feasibility, listing, and medical management. Chronic infection, irreversible elevation of pulmonary vascular resistance, and intractable disease in other organ systems may all be contraindications for transplantation. The United Network for Organ Sharing has recently changed its listing guidelines. Adolescent donors are now preferentially, to some extent, allocated to adolescent recipients. Management of pediatric patients awaiting cardiac transplantation encompasses optimization of cardiac output through the use of vasodilators and oral and intravenous inotropic agents. For those patients listed for transplantation who have single ventricle lesions, such as hypoplastic left heart syndrome, management of heart failure also includes balancing systemic and pulmonary blood flows. Mechanical support of the circulation with extracorporeal membrane oxygenation or ventricular assist devices can be used as a bridge to transplant in pediatric patients.

Keywords: Cardiac transplantation; Pediatrics; Heart failure

1. Introduction

The process of cardiac transplantation can be divided into three phases: (1) the preoperative time from initial referral, through evaluation and waiting for a donor heart; (2) the operative procedure; and (3) life after transplantation with chronic immunosuppression. The first preoperative phase of the process can itself be divided into three parts. Preoperative assessment is critical to determine the feasibility of cardiac transplantation in a particular patient. Once feasibility is established, the patient is listed for transplantation based on criteria of the severity of illness established in the US by the United Network for Organ Sharing (UNOS). Once a patient is listed for transplantation, therapy is designed to maintain cardiovascular stability until an acceptable donor heart is available.

2. Preoperative assessment

The evaluation of potential heart transplant recipients is usually directed at determining if there are associated medical problems that would preclude transplantation or require special arrangements at the time of surgery. Previous consensus panels have published guidelines [1–3] of absolute and relative contraindications for cardiac transplantation. With increasing experience, most ‘absolute’ contraindications have become relative, and today there are very few children with end-stage heart failure who are unacceptable candidates for cardiac transplant [4].

In infants and children with congenital or acquired cardiovascular abnormalities, the technical challenges
of body situs, pulmonary arteries, atria, and systemic and pulmonary venous return have been largely overcome [5–8]. With the increasing recognition of genetic causes of many pediatric cardiomyopathies [9], genetic and metabolic evaluation is an important part of the transplant assessment. A small number of these metabolic problems may be treatable with metabolic supplements such as carnitine. Other potentially reversible causes of cardiomyopathy should be excluded, such as anomalous left coronary arising from the pulmonary artery or incessant tachyarrhythmias. Because skeletal muscle disease often accompanies cardiomyopathy [10], formal evaluation of skeletal muscle strength and tone can be useful, and sometimes muscle biopsy is indicated. Cardiac catheterization is generally performed before transplantation to exclude irreversible pulmonary vascular disease, which can result in fatal acute graft failure after transplantation. This problem is addressed in detail in a separate paper in this review.

Transplant medical evaluations are designed to identify potential exclusion criteria, such as irreversible disease in the lungs, liver, kidney, or central nervous system, and to recognize acute and chronic infections, which may adversely affect the surgical outcome. Pre-existing medical problems such as diabetes, obesity, and peptic ulcer disease may be exacerbated after transplantation by the use of corticosteroids, although diabetics without end-organ damage have been transplanted successfully [11]. Table 1 illustrates a typical transplant evaluation protocol.

Chronic viral infections such as HIV [12] and hepatitis B [13] have been associated with poor outcomes after transplantation, and they are generally con-

<table>
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<th>Table 1</th>
<th>Pediatric cardiac transplantation evaluation protocol</th>
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| **Cardiology** | Chest X-ray  
EKG  
Echocardiogram  
Exercise stress test including maximal oxygen consumption  
Cardiac catheterization and angiography  
may include endomyocardial biopsy  
may include drug studies to manipulate cardiac index and pulmonary vascular resistance |
| **Hematology** | Complete blood count and differential  
Prothrombin and partial thromboplastin time |
| **Blood chemistry** | Serum electrolytes, magnesium, calcium, phosphorus  
Serum transaminases, bilirubin, albumin, total protein, alkaline phosphatase, cholesterol, triglycerides, uric acid, lactate dehydrogenase, creatine phosphokinase |
| **Renal** | Urinalysis  
Serum blood urea nitrogen and creatinine  
24-h urine collection for creatinine clearance |
| **Pulmonary** | Pulmonary function tests |
| **Serology** | CMV, EBV, varicella, herpes, hepatitis, HIV titers |
| **Cultures** | Bacterial and viral blood, throat, urine, stool, sputum parasites, fungus |
| **Immunology** | HLA typing  
Panel reactive antibody (titer and type of anti-HLA antibodies) |
| **Neurology** | CT or MRI scan  
EEG |
| **Consultations** | Neurology (also to exclude associated skeletal muscle disease)  
Genetics  
Psychology  
Physical/occupational therapy  
Dietetics  
Social worker  
Financial/health insurance coordinator |
sidered as contraindications for transplantation. The presence of Hepatitis C infection is more controversial. These patients have undergone cardiac transplantation in the past, but recent evidence [14,15] suggests that they are at risk for developing potentially fatal liver disease within the first 5 years after transplant. Thus, Hepatitis C infection can be a relative contraindication to transplantation, or it can mandate the exclusive use of a Hepatitis C positive donor.

High panel reactive antibody titers (usually > 20%) identify patients with sensitivity to a large number of HLA antigens. Preformed anti-HLA antibodies may attack and damage the graft (hyperacute rejection) within hours after the transplant procedure, and they have been associated with a greater risk of rejection [16]. This phenomenon is especially relevant to patients with congenital heart disease. A recent study [17] has demonstrated that congenital heart surgery using homograft material (valves, aorta, pulmonary artery) is associated with the development of high titers of anti-HLA antibodies in survivors. The use of mechanical ventricular support devices has also been followed by rapid sensitization to HLA antigens [18]. Once identified, patients with high panel reactive antibody titers can be successfully transplanted with a prospective donor cross-match or more recently by lowering the antibody titer with intravenous gamma globulin and/or plasmapheresis given in the perioperative period [19–21].

Children with a past history of malignancy can be transplanted successfully [22], although in patients with a recent history (< 5 years) of malignancy, clearance of the risks of recurrence should be established by a pediatric oncology consultation. A preoperative psychosocial evaluation is particularly important. In adult centers a recent history of smoking or substance abuse is usually considered a relative contraindication to transplantation [1–3]. Pre-existing psychosocial problems also need to be identified because of their association with increased morbidity after transplantation [23,24]. The broad continuum of functional ability of children with chromosomal anomalies requires assessment on a case-by-case basis, rather than by arbitrary exclusion.

3. Listing

In the US, UNOS is under contract with the federal government to organize and maintain a list of potential heart transplant recipients, children and adults, and to facilitate donor matching. Allocation of donor hearts to recipients is determined by the severity of the patient’s illness, the ABO blood type, the distance of a patient from a donor, and the duration on the transplant list for the current severity of illness. In the past there were two grades of status: Status 1 which required a patient to be on inotropic support and in an intensive care unit; and Status 2 which included all other conditions and characteristics. All infants listed at less than 6 months of age were considered Status 1 since most of them had hypoplastic left heart syndrome and were prostaglandin-dependent to stabilize the systemic circulation.

In January 1999 the listing hierarchy was modified to improve allocation of donor hearts to the sickest patients. Table 2 summarizes these changes for pediatric recipients. Status 1A contains patients receiving mechanical ventilatory or circulatory support, multiple high-dose inotropes, or infants younger than 6 months of age who have severe labile pulmonary hypertension (> 50% systemic). Status 1B identifies patients on a single low-dose inotrope, infants less than 6 months of age who are not Status 1A, or patients with growth failure. Patients with blood type A no longer receive type O donors because of the comparatively longer waiting times for O patients who can be matched only to O donors, unless no suitable type O donors are available. To match donors to the ages of pediatric recipients, hearts from adolescent donors (11–18 years old) are allocated preferentially to pediatric recipients within a given status.

4. Maintenance of suitability for transplantation

Once listed, patients awaiting cardiac transplantation often develop progressive cardiac insufficiency. Consequently, much of the management of the patient before transplantation involves the optimal treatment of heart failure. Stevenson has coined the term ‘tailored therapy’ [26] to describe the process whereby

<table>
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<th>Table 2</th>
<th>Revised UNOS transplant list status categories</th>
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<tr>
<td>Status 1A meets at least one of these criteria:</td>
<td>Requires assistance with a ventilator, balloon pump, or mechanical assist device including ECMO</td>
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<td>Requires infusion of high dose (e.g. dobutamine &gt; 7.5 μg/kg/min or milrinone &gt; 0.5 μg/kg/min) or multiple inotropes</td>
<td>A patient &lt; 6 months old exhibiting reactive pulmonary hypertension &gt; 50% systemic levels</td>
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<tr>
<td>Any patient whose life expectancy is judged to be &lt; 14 days, such as patient with refractory arrhythmia.</td>
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<td>Status 1B meets at least one of these criteria:</td>
<td>Requires infusion of low-dose (less than Status 1A dose) single inotrope</td>
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<tr>
<td>Less than 6 months old not meeting Status 1A criteria</td>
<td>Growth failure (&lt; 5th percentile for weight and/or height, or loss of 1.5 S.D. of expected growth) due to heart disease</td>
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<tr>
<td>Status 2 covers all other active patients</td>
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vasodilator and diuretic drugs are chosen and dosed according to the specific hemodynamics of an individual patient. Most pediatric patients in heart failure are managed with combinations of digoxin, diuretics, and ACE inhibitors, but if there is persistent elevation of systemic vascular resistance, further improvement in cardiac output usually can be obtained by increasing vasodilatation. During pretransplant evaluations cardiac catheterization is useful for measuring pulmonary and systemic resistance to determine if vasodilator therapy can be increased. If systemic resistance is normal or low, increasing vasodilatation can lead to decreased blood pressure and peripheral organ perfusion, which can produce complications such as renal insufficiency. Increased vasodilatation can be accomplished by increasing the dose of ACE inhibitors to maximal levels [3,27,28], although extraordinarily high doses can be associated with drug-induced renal failure. Additional vasodilators can be added to ACE inhibitors to increase afterload reduction. In the past, long-acting nitrates and hydralazine have been used [28], although recent study [29] suggests that adding specific angiotensin II blockers to ACE inhibitors may also be beneficial.

Recent studies in adults have demonstrated that the addition of beta-blockers such as metoprolol and carvedilol may improve heart failure symptoms and survival [30]. Most of these studies have been done in patients with moderate heart failure, not sick enough to be considered for transplantation. However, a recent study [31] demonstrated that beta blockers could lead to improvement in NYHA class IV adults if introduced with inotropes, although drug-related side effects were high. Experiences with beta-blockers in infants and children with heart failure are limited [32] and their efficacy remains to be defined in patients listed for transplantation.

Alternative surgical therapies for left ventricular dysfunction have been introduced using the concept of partial left ventriculectomy and mitral valve surgery (the ‘Batista’ procedure) to decrease left ventricular cavity size. This improves left ventricular function by decreasing wall stress and reduces left ventricular volume [33]. Adult transplant centers have explored the use of this surgery with mixed results [34,35]. While its proper place in the management of patients with left ventricular dysfunction remains to be defined, its use in infants [36,37] was associated with short-term improvements in left ventricular function.

The exacerbation or reappearance of symptoms of heart failure in children already taking oral digoxin, diuretics, and ACE inhibitors will often lead to a temporary use of inotropes. The most frequently used inotropes are beta agonists such as dobutamine and phosphodiesterase inhibitors such as milrinone [38]. Milrinone also has significant vasodilator properties and should be used with caution in patients with low systemic vascular resistance. The beneficial hemodynamic effects of these medications will persist for days after their cessation. In adults with heart failure this effect has led to their use as intermittent, ambulatory therapy to avoid hospitalization [39]. In pediatric patients the ‘successful’ weaning from inotropic support cannot be accomplished in hours, but requires several days to identify those children who have developed a need for chronic inotropic therapy. The addition of chronic inotropic support improves a patient’s chances for a donor heart by moving them ‘up the list’. Their use should be reserved, however, for patients who clearly are dependent on them for improving symptoms of heart failure, since controlled studies in adults have found an increased mortality with the chronic use of dobutamine and milrinone [40,41].

Within the past few years the use of mechanical support devices to augment cardiac output has dramatically changed the outlook for adult patients who remain unstable despite maximal pharmacological support. Implantable left ventricular assist devices (LVAD) (Novacor, Heart Mate) can be used with low morbidity and can be managed in an outpatient setting with a portable battery pack [42]. The usefulness of these devices in listed adult patients with severe heart failure is affirmed by the improvements seen in UNOS status from 1A to 1B within 4 weeks after implantation [25]. Unfortunately the size of the device limits their use in children, but they are an attractive option for larger adolescents. External VADS (Thoratec) have been used in pediatric patients as small as 20 kg [43], but ambulation is very difficult. An experimental VAD for very small children (Medos) is undergoing trials in Germany with promising initial results [44]. For more than a decade non-pulsatile cardiac support with extracorporeal circulation (ECMO) has been used for mechanical circulatory support in infants and children [45,46]. However, ECMO is limited by a relatively short-term effectiveness (days to weeks) due to increasing risks of sepsis, bleeding, and secondary end-organ dysfunction with longer use.

In addition to therapies to maximize cardiac output, careful attention to nutrition and physical activity is important in patients awaiting transplantation. Children with end-stage heart failure are frequently nauseous and anorexic and have minimal physical activity. This combination can lead to skeletal muscle breakdown and atrophy which can exacerbate symptoms of heart failure [47]. Hyperalimentation may be required to maintain adequate nutritional support and a formal physical therapy program is helpful in minimizing muscle weakness and atrophy. In patients with severely depressed systolic ventricular function,
the frequency of mural thrombus formation and associated pulmonary and systemic embolus [48,49] justifies the prophylactic use of anticoagulants such as Warfarin while awaiting transplant.

Arrhythmias frequently complicate the management of patients in heart failure awaiting transplantation. Chronic tachycardia can lead to heart failure and mimic the findings of a dilated cardiomyopathy. Before and after transplantation cardiomyopathies and congenital heart disease can be associated with brady- and tachyarrhythmias, in addition to pump failure. For patients with bradyarrhythmias, the use of synchronous DDD pacing, rather than asynchronous ventricular pacing, can augment stroke volume and improve cardiac index. In pretransplant patients with supraventricular arrhythmias, ablation of bypass tracts or re-entrant circuits can be helpful in eliminating the risk of sudden cardiac decompensation. Ventricular ectopy and non-sustained ventricular tachycardia are commonly observed in patients with myocardial failure, and though often asymptomatic, they are associated with increased mortality and sudden death [50,51]. The treatment of asymptomatic ventricular ectopy, however, has not been associated with improved survival [52]. Unless they are caused by electrolyte disorders, the need to treat these arrhythmias is somewhat questionable because many of the antiarrhythmic agents can produce negative inotropic and proarrhythmic effects and significant symptomatic side effects. Given its efficacy and tendency to improve ejection fraction, amiodarone may be the best antiarhythmic for patients with end-stage heart failure and symptomatic arrhythmias [53]. Symptomatic ventricular arrhythmias, however, may be best treated with an implantable defibrillator [54].

Patients with single ventricles listed for transplantation present unique management problems. For those with defects such as hypoplastic left heart syndrome, whose pulmonary and systemic circulations are associated with unrestricted pulmonary flow, the management of heart failure also includes balancing the ratio of systemic to pulmonary blood flow to minimize the risks of excessive pulmonary flow. The postoperative strategies used after the Norwood procedure to increase pulmonary vascular resistance (forced hypoxia or hypercarbia) [55,56] or to decrease systemic vascular resistance [57] can also be applied to patients awaiting transplant. The long-term use of central lines in infants can be associated with infection and with vena caval thrombosis, a significant complication in children whose management requires repeated cardiac catheterization. Restriction of pulmonary venous return at the level of the foramen ovale, if mild, can help to decrease pulmonary blood flow, but it can also lead to intractable hypoxia [58]. In this situation a limited increase in the size of the foramen ovale may help to relieve symptoms [59].

5. Conclusions

Within the past 15 years, cardiac transplantation for pediatric patients with end-stage cardiac disease has evolved from a heroic therapy to mainstream management. Very few children who can benefit from transplantation will have insurmountable problems that preclude the surgery. Recent changes with listing hierarchies in the US have evolved to maximize donor availability for children and adolescents. The mortality while waiting for transplantation remains, especially in infants with hypoplastic left heart syndrome [60]. However, just as increasing experience with transplantation surgery has lead to better surgical outcomes, experienced pediatric transplant centers have improved upon both the management and the survival rates of infants and children awaiting an appropriate donor heart [61].

References


