I. Description

A heart transplant consists of replacing a diseased heart with a healthy donor heart. Transplantation is used for patients with refractory end-stage cardiac disease.

Background

Heart failure may be the consequence of a number of differing etiologies, including ischemic heart disease, cardiomyopathy, or congenital heart defects. The reduction of cardiac output is considered to be severe when systemic circulation cannot meet the body’s needs under minimal exertion. Heart transplantation improves quality of life and has patient survival rates at 1, 5, and 10 years of 88%, 74%, and 55%, respectively. (1)

The shortage of donor hearts has led to the use of transplantation in those most likely to derive benefit. At the same time, advances in medical and device therapy for patients with advanced heart failure has improved the survival of patients awaiting heart transplantation. Due to the variable natural history of heart failure, functional and hemodynamic parameters have been utilized to estimate prognosis.

In 2009, 2,211 heart transplants were performed in the U.S. There were 2,997 patients on the waiting list at the end of 2009. (1)

II. Policy

Human heart transplantation is covered (subject to Administrative Guidelines) for selected adults and children with end-stage heart failure when patient selection criteria are met.

Adult Patients
A. Accepted Indications for Transplantation

1. For hemodynamic compromise due to heart failure demonstrated by any of the following three bulleted items, or
   - Maximal V02 (oxygen consumption) <10 ml/kg/min with achievement of anaerobic metabolism
   - Refractory cardiogenic shock
   - Documented dependence on intravenous inotropic support to maintain adequate organ perfusion
2. Severe ischemia consistently limiting routine activity not amenable to bypass surgery or angioplasty, or
3. Recurrent symptomatic ventricular arrhythmias refractory to ALL accepted therapeutic modalities.

B. Probable Indications for Cardiac Transplantation

1. Maximal VO2 <14 ml/kg/min and major limitation of the patient’s activities, or
2. Recurrent unstable ischemia not amenable to bypass surgery or angioplasty, or
3. Instability of fluid balance/renal function not due to patient noncompliance with regimen of weight monitoring, flexible use of diuretic drugs, and salt restriction

C. The following conditions are inadequate indications for transplantation unless other factors as listed above are present.

1. Ejection fraction <20%
2. History of functional class III or IV symptoms of heart failure
3. Previous ventricular arrhythmias
4. Maximal VO2 >15 ml/kg/min

Pediatric Patients

A. Patients with heart failure with persistent symptoms at rest who require one or more of the following:
   - Continuous infusion of intravenous inotropic agents, or
   - Mechanical ventilatory support, or
   - Mechanical circulatory support

B. Patients with pediatric heart disease with symptoms of heart failure who do not meet the above criteria but who have:
   - Severe limitation of exercise and activity (if measurable, such patients would have a peak maximum oxygen consumption <50% predicted for age and sex); or
   - Cardiomyopathies or previously repaired or palliated congenital heart disease and significant growth failure attributable to the heart disease; or
• Near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator; or
• Restrictive cardiomyopathy with reactive pulmonary hypertension; or
• Reactive pulmonary hypertension and potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future; or
• Anatomical and physiological conditions likely to worsen the natural history of congenital heart disease in infants with a functional single ventricle; or
• Anatomical and physiological conditions that may lead to consideration for heart transplantation without systemic ventricular dysfunction.

III. Policy Guidelines

Potential contraindications subject to the judgment of the transplant center:

1. Known current malignancy, including metastatic cancer
2. Recent malignancy with high risk of recurrence
3. Untreated systemic infection making immunosuppression unsafe, including chronic infection
4. Other irreversible end-stage disease not attributed to heart or lung disease
5. History of cancer with a moderate risk of recurrence
6. Systemic disease that could be exacerbated by immunosuppression
7. Psychosocial conditions or chemical dependency affecting ability to adhere to therapy

Policy Specific

8. Pulmonary hypertension that is fixed as evidenced by pulmonary vascular resistance (PVR) greater than 5 Woods units, or trans-pulmonary gradient (TPG) greater than or equal to 16 mm/Hg*
9. Severe pulmonary disease despite optimal medical therapy, not expected to improve with heart transplantation*

*Some patients may be candidates for combined heart-lung transplantation.

Patients must meet the United Network for Organ Sharing (UNOS) guidelines for 1A, 1B, or 2 Status and not currently be Status 7.

Cardiac Specific

The United Network for Organ Sharing (UNOS) prioritizes donor thoracic organs according to the severity of illness, with those patients who are most severely ill (status 1A) given highest priority in allocation of the available organ as follows (2):

Adult patients (18 years of age or older)
Status 1A

A patient is admitted to the listing transplant center hospital and has at least one of the following devices or therapies in place:

A. Mechanical circulatory support for acute hemodynamic decompensation that includes at least one of the following:
   1. Left and/or right ventricular assist device implanted
   2. Total artificial heart
   3. Intra-aortic balloon pump: or
   4. Extracorporeal membrane oxygenator (ECMO)
B. Mechanical circulatory support
C. Mechanical ventilation
D. Continuous infusion of inotropes and continuous monitoring of left ventricular filling pressures
E. If criteria A, B, C, D are not met, such status can be obtained by application to the applicable Regional Review Board

Status 1B

A patient has at least one of the following devices or therapies in place:

A. left and/or right ventricular device implanted
B. continuous infusion of intravenous inotropes

A patient that does not meet Status 1A or 1B is listed as Status 2.

Pediatric patients

A candidate listed as Status 1A meets at least one of the following criteria:

- Requires assistance with a ventilator;
- Requires assistance with a mechanical assist device (e.g., ECMO);
- Requires assistance with a balloon pump;
- A candidate younger than 6 months old with congenital or acquired heart disease exhibiting reactive pulmonary hypertension at greater than 50% of systemic level. Such a candidate may be treated with prostaglandin E (PGE) to maintain patency of the ductus arteriosus;
- Requires infusion of high dose (e.g., dobutamine ≥7.5 mcg/kg/min or milrinone ≥0.5 mcg/kg/min) or multiple inotropes (e.g., addition of dopamine at ≥5.0 mcg/kg/min); or

A candidate who does not meet the criteria specified in (A), (B), (C), (D), or (E) may be listed as Status 1A if the candidate has a life expectancy without a heart transplant of less than 14 days, such as due to refractory arrhythmia.
A candidate listed as Status 1B meets at least one of the following criteria:

- Requires infusion of low dose single inotropes (e.g., dobutamine or dopamine < 7.5 mcg/kg/min);
- Younger than 6 months old and does not meet the criteria for Status 1A; or
- Growth failure, i.e., greater than 5th percentile for weight and/or height, or loss of 1.5 standard deviations of expected growth (height or weight) based on the National Center for Health Statistics for pediatric growth curves.

A candidate who does not meet the criteria for Status 1A or 1B is listed as Status 2.

Note: Pediatric heart transplant candidates who remain on the waiting list at the time of their 18th birthday without receiving a transplant continue to qualify for medical urgency status based upon the pediatric criteria.

Status 7 patients are considered temporarily unsuitable to receive a thoracic organ transplant.

IV. Administrative Guidelines

A. Precertification is required. To precertify, fill out HMSA’s Precertification Request and fax or mail the form as indicated.

B. Applicable codes:

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>33940</td>
<td>Donor cardiectomy (including cold preservation)</td>
</tr>
<tr>
<td>33944</td>
<td>Backbench standard preparation of cadaver donor heart allograft prior to transplantation, including dissection of allograft from surrounding tissues to prepare aorta, superior vena cava, inferior vena cava, pulmonary artery, and left atrium for implantation</td>
</tr>
<tr>
<td>33945</td>
<td>Heart transplant, with or without recipient cardiectomy</td>
</tr>
</tbody>
</table>

V. Rationale

Literature Review

This policy was originally created in 1996 and updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period September 2010 through September 2011. Due to the nature of the population, there are no randomized controlled trials (RCTs) comparing heart transplantation with alternatives, including ventricular assist devices. Systematic reviews are based on case series and registry data. The extant RCTs compare surgical technique, infection prophylaxis, or immunosuppressive therapy and are not germane to this policy. The following is a summary of evidence based on registries, case series, and expert opinion.

Prioritization of candidates
In contrast to the 1980s when the majority of heart transplant recipients were sick but stable patients waiting at home, the majority of heart transplant recipients are now hospitalized Status 1 patients at the time of transplant. This shift has occurred due to the increasing demand on the scarce resource of donor organs resulting in an increased waiting time for donor organs. Patients initially listed as a Status 2 candidate may deteriorate to a Status 1 candidate before a donor organ becomes available.

At the same time, as medical and device therapy for advanced heart failure has improved, some patients on the transplant list will recover enough function to become delisted. In 2007, Lietz and Miller reported on patient survival on the heart transplant waiting list, comparing the era between 1990 and 1994 to the era of 2000 to 2005. (3) One-year survival for UNOS Status 1 candidates improved from 49.5% to 69.0%. Status 2 candidates fared even better, with 89.4% surviving 1 year compared to 81.8% in the earlier time period.

In 2010, Johnson and colleagues reported on waiting list trends in the U.S. between 1999 and 2008. (4) They noted an increasing trend of adult patients with congenital heart disease and retransplantation. The proportion of patients listed as Status 1 continued to increase, even as waiting list and post-transplant mortality for this group decreased. Meanwhile, Status 2 patients have decreased as a proportion of all candidates. Completed transplants have trended toward the extremes of age, with more infants and patients older than age 65 years having transplants in recent years.

As a consequence, aggressive treatment of heart failure has been emphasized in recent guidelines. Prognostic criteria have been investigated to identify patients who have truly exhausted medical therapy and thus are likely to derive the maximum benefit for heart transplantation. Maximal oxygen consumption (VO2), which is measured during maximal exercise, is one measure that has been suggested as a critical objective criterion of the functional reserve of the heart. The American College of Cardiology (ACC) has adopted maximal VO2 as one criterion for patient selection. (5) Studies have suggested that transplantation can be safely deferred in those patients with a maximal VO2 of greater than 14 mL/kg/min. The importance of the maximal VO2 has also been emphasized by an American Heart Association Scientific Statement addressing heart transplant candidacy. (6) In past years, a left ventricular ejection fraction (LVEF) of less than 20% or a New York Heart Association (NYHA) Class III or IV status may have been used to determine transplant candidacy. However, as indicated by the ACC criteria, these measurements are no longer considered adequate to identify transplant candidates. These measurements may be used to identify patients for further cardiovascular workup but should not be the sole criteria for transplant.

Methods other than maximal VO2 have been proposed as predictive models in adults. (7-10) The Heart Failure Survival Scale (HFSS) and Seattle Heart Failure Model (SHFM) are two examples. In particular, the SHFM provides an estimate of 1-, 2-, and 3-year survival with the use of routinely obtained clinical and laboratory data. Information regarding pharmacologic and device usage is incorporated into the model, permitting some estimation of effects of current, more aggressive heart failure treatment strategies. In 2006, Levy and colleagues (11) introduced the model using
multivariate analysis of data from the PRAISE1 heart failure trial (n=1,125). Applied to the data of 5 other heart failure trials, the SHFM correlated well with actual survival (r: 0.98, standard error of the estimate=+3). The SHFM has been validated in both ambulatory and hospitalized heart failure populations (12-14) but with a noted underestimation of mortality risk, particularly in blacks and device recipients. (15,16) None of these models has been universally adopted by transplant centers.

**Pediatric considerations**

Noting that children listed for heart transplantation have the highest waiting list mortality of all solid organ transplant patients, Almond and colleagues analyzed data from the U.S. Scientific Registry of Transplant Recipients to determine if the pediatric heart allocation system, as revised in 1999, prioritizes patients optimally and to identify high-risk populations that may benefit from pediatric cardiac assist devices. (17) Of 3,098 children (younger than 18 years of age) listed between 1999 and 2006, a total of 1,874 (60%) were listed as Status 1A. Of those, 30% were placed on ventilation and 18% were receiving extracorporeal membrane oxygenation. Overall, 533 (17%) died, 1,943 (63%) received transplants, 252 (8%) recovered, and 370 (12%) remained listed. The authors found that Status 1A patients are a heterogeneous population with large variation in mortality based on patient-specific factors. Predictors of waiting list mortality included extracorporeal membrane oxygenation support (hazard ratio [HR]: 3.1), ventilator support (HR: 1.9), listing status 1A (HR: 2.2), congenital heart disease (HR: 2.2), dialysis support (HR: 1.9), and non-white race/ethnicity (HR: 1.7). The authors concluded that the pediatric heart allocation system captures medical urgency poorly, specific high-risk subgroups can be identified, and further research is needed to better define the optimal organ allocation system for pediatric heart transplantation.

In 2010, Patel and colleagues presented a retrospective review of echocardiography and serum markers as a predictor of death or need for transplantation in newborns, children, and young adults with heart failure. (18) A total of 99 children with 139 admissions were evaluated on LVEF and tricuspid regurgitation, as well as on various serum markers for their predictive ability of death or need for transplantation in a stepwise multivariate Cox regression model. While brain natriuretic peptide (BNP) and tricuspid regurgitation were not predictive of need for transplantation, ejection fraction and lymphocytosis were predictive (odds ratio 0.94, 95% confidence interval [CI]: 0.90-0.98 for ejection fraction; odds ratio 5.40, 95% CI: 1.67–17.4 for lymphocytosis). Serum levels of creatinine and sodium were also predictive. Clinical prediction rules based on these findings have not been compared to current strategies and await clinical validation.

Another retrospective review of pediatric cardiac transplantation patients was published by Auerbach and colleagues in 2011. (19) A total of 191 patients who underwent primary heart transplantation at a single center in the United States were included; their mean age was 9.7 years (range, 0 to 23.6 years). Overall graft survival was 82% at 1 year and 68% at 5 years; the most common causes of graft loss were acute rejection and graft vasculopathy. Overall patient survival was 82% at 1 year and 72% at 5 years. In multivariate analysis, the authors found that congenital heart disease (HR: 1.6, 95% CI: 1.02-2.64) and requiring mechanical ventilation at the time of
transplantation (HR: 1.6, 95% CI: 1.13-3.10) were both significantly independently associated with an increased risk of graft loss. Renal dysfunction was a significant risk factor in univariate analysis but was not included in the multivariate model due to the small study group. Limitations of the study include that it was retrospective and conducted in only one center.

**Mortality after heart transplant**

In 2008, British researchers used data from a national audit to examine the effect of heart transplantation on heart failure mortality in the United Kingdom. (20) Records of 2,219 adults listed for transplantation between April 1995 and October 2003, and followed up to June 2007 were analyzed. In total, 1,613 patients received a transplant, 90.6% within 1 year of listing. In all, 620 patients died after surgery, 310 within 1 year. Transplantation conferred a survival benefit for both ambulatory and non-ambulatory patients. Overall survival was 77.6% for ambulatory and 75.4% for non-ambulatory patients at 3 years’ post-transplant (p=0.68), The sicker, non-ambulatory patients received this benefit in the shortest time; a net survival benefit was seen after 26 days, while the ambulatory group received a net benefit after 274 days.

A 2011 study by Jalowiec and colleagues compared clinical outcomes in sex-matched and sex-mismatched heart transplant recipients. (21) They retrospectively reviewed data from 347 heart transplant recipients; 237 (78.7%) received a heart from a same-sex donor, 40 (11.5%) cases involved a female donor and male recipient, and 34 (9.8%) cases involved a male donor and female recipient. There was not a statistically significant difference in the mortality rate during the first month post-transplant between the sex-matched and either sex-mismatched group. In adjusted analyses, 2 of the other 9 study outcomes differed significantly among the 3 groups. The male donor-female recipient group had significantly more treated rejection episodes during the first year post-transplant and significantly more days of rehospitalization after the initial discharge than either of the other 2 groups. The incidence of steroid-induced diabetes, cardiac allograft vasculopathy, non-skin cancers, number of IV-treated infections post-transplant, and initial hospital length of stay were not significantly different among groups.

**Potential contraindications**

Individual transplant centers may differ in their guidelines, and individual patient characteristics may vary within a specific condition. In general, heart transplantation is contraindicated in patients who are not expected to survive the procedure or in whom patient-oriented outcomes, such as morbidity or mortality, are not expected to change due to comorbid conditions unaffected by transplantation e.g., imminently terminal cancer or other disease. Further, consideration is given to conditions in which the necessary immunosuppression would lead to hastened demise, such as active untreated infection. However, stable chronic infections have not always been shown to reduce life expectancy in heart transplant patients.

**Malignancy**
Concerns regarding a potential recipient’s history of cancer were based on the observation of significantly increased incidence of cancer in kidney transplant patients. (22) In fact, carcinogenesis is 2 to 4 times more common in heart transplant patients, likely due to the higher doses of immunosuppression necessary for the prevention of allograft rejection, the majority of which are skin cancers. (23) The incidence of de novo cancer in heart transplant patients approaches 26% at 8 years post-transplant. For renal transplant patients who had a malignancy treated prior to transplant, the incidence of recurrence ranged from zero to more than 25% depending on the tumor type. (24, 25) However, it should be noted that the availability of alternate treatment strategies informs recommendations for a waiting period following high-risk malignancies: in renal transplant, a delay in transplantation is possible due to dialysis; end-stage heart failure patients may not have another option. A small study (n=33) of survivors of lymphoproliferative cancers who subsequently received cardiac transplant had 1-, 5-, and 10-year survival rates of 77%, 64%, and 50%, respectively. (26) By comparison, overall 1-, 5-, and 10-year survival rates are expected to be 88%, 74%, and 55%, respectively, for the general transplant candidate. The evaluation of a candidate who has a history of cancer must consider the prognosis and risk of recurrence from available information including tumor type and stage, response to therapy, and time since therapy was completed. Although evidence is limited, patients in whom cancer is thought to be cured should not be excluded from consideration for transplant. UNOS has not addressed malignancy in current policies.

HIV

Solid organ transplant for patients who are HIV-positive (HIV+) has been controversial, due to the long-term prognosis for human immunodeficiency virus (HIV) positivity and the impact of immunosuppression on HIV disease. Although HIV+ transplant recipients may be a research interest of some transplant centers, the minimal data regarding long-term outcome in these patients consist primarily of case reports and abstract presentations of liver and kidney recipients. Nevertheless, some transplant surgeons would argue that HIV positivity is no longer an absolute contraindication to transplant due to the advent of highly active antiretroviral therapy (HAART), which has markedly changed the natural history of the disease.

In March 2009, the Organ Procurement Transfer Network (OPTN) revised its policies on HIV status in recipients. It reiterates an earlier position that: “A potential candidate for organ transplantation whose test for HIV is positive but who is in an asymptomatic state should not necessarily be excluded from candidacy for organ transplantation, but should be advised that he or she may be at increased risk of morbidity and mortality because of immunosuppressive therapy.” (27)

In 2006, the British HIV Association and the British Transplantation Society Standards Committee published guidelines for kidney transplantation in patients with HIV disease. (28) These criteria may be extrapolated to other organs:

- CD4 count >200 cells/mm for at least 6 months
- Undetectable HIV viremia less than 50 HIV-1 RNA copies/ml) for at least 6 months
- Demonstrable adherence and a stable HAART regimen for at least 6 months
• Absence of AIDS-defining illness following successful immune reconstitution after HAART.

Other

In 2008, Weiss and associates studied retrospective UNOS data on 14,401 patients who had received a heart transplant. (29) Independent factors associated with statistically significantly worse outcomes were age greater than 60 years, diabetes, and hypertension. Older patients had more infections (26% vs. 23%, p<0.001) and longer hospital stays (21 vs. 19 days, p<0.001, respectively) but had lower rates of rejection (34% vs. 43%, p<0.001, respectively) as compared with younger recipients. However, 1-year mortality in the older patients remained acceptable at 84%, compared to 87% in the younger group.

Costard-Jackle and Fowler described postoperative complications in patients with pulmonary hypertension. (30) A fixed pulmonary vascular resistance (PVR) greater than 4 Wood units has been associated with right ventricular failure in the immediate post-transplant period. However, current medications can reduce the PVR in some patients; they can be considered for heart transplant. Patients with end-stage heart disease and end-stage lung disease, including pulmonary hypertension, can benefit from combined heart-lung transplantation. Patients must have both organs available, however, prior to transplantation.

Summary

The literature, consisting of case series and registry data, continues to demonstrate that heart transplantation provides a survival benefit in appropriately selected patients, compared to the exceedingly poor expected survival without transplantation. Despite an improvement in prognosis for many patients with advanced heart disease, heart transplant remains a viable treatment for those who have exhausted other medical or surgical remedies, yet remain in end-stage disease. Heart transplantation is contraindicated in patients in whom the procedure is expected to be futile due to comorbid disease or in whom post-transplantation care is expected to significantly worsen comorbid conditions.

Practice Guidelines and Position Statements

The accepted indications, probable indications, and contraindications for heart transplantation listed in the policy and guideline sections of this policy reflect the 2005 update of the ACC/AHA joint statement on diagnosis and management of chronic heart failure in the adult. They are unchanged in the 2009 update of the ACC/AHA statement. (5)

The International Society for Heart and Lung Transplantation (ISHLT) recommended in a 2004 statement that children with the following conditions should be evaluated for heart transplantation (31):
Diastolic dysfunction that is refractory to optimal medical/surgical management because they are at high risk of developing pulmonary hypertension and of sudden death (based on level of evidence B [a single randomized trial or multiple non-randomized trials])

Advanced systemic right ventricular failure (Heart Failure stage C described as patients with underlying structural or functional heart disease and past or current symptoms of heart failure) that is refractory to medical therapy (level of evidence C [primarily expert consensus opinion]).

The AHA Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group stated in 2007 that, based on level B (non-randomized studies) or level C (consensus opinion of experts), heart transplantation is indicated for pediatric patients as therapy for the following indications (32):

- stage D heart failure (interpreted as abnormal cardiac structure and/or function, continuous infusion of intravenous inotropes, or prostaglandin E1 to maintain patency of a ductus arteriosus, mechanical ventilatory and/or mechanical circulatory support) associated with systemic ventricular dysfunction in patients with cardiomyopathies or previous repaired or palliated congenital heart disease

- stage C heart failure (interpreted as abnormal cardiac structure and/or function and past or present symptoms of heart failure) associated with pediatric heart disease and severe limitation of exercise and activity, in patients with cardiomyopathies or previously repaired or palliated congenital heart disease and heart failure associated with significant growth failure attributable to heart disease, pediatric heart disease with associated near sudden death and/or life-threatening arrhythmias untreatable with medications or an implantable defibrillator, or in pediatric restrictive cardiomyopathy disease associated with reactive pulmonary hypertension,

- the guideline states that heart transplantation is feasible in the presence of other indications for heart transplantation, in patients with pediatric heart disease and an elevated pulmonary vascular resistance index >6 Woods units/m2 and/or a transpulmonary pressure gradient >15 mm Hg if administration of inotropic support or pulmonary vasodilators can decrease pulmonary vascular resistance to <6 Woods units/m2 or the transpulmonary gradient to <15 mm Hg.

Medicare National Coverage

Cardiac transplantation is covered under Medicare when performed in a facility that is approved by Medicare as meeting institutional coverage criteria. (33)

The Centers for Medicare and Medicaid Services (CMS) has stated that under certain limited cases, exceptions to the criteria may be warranted if there is justification and if the facility ensures safety and efficacy objectives.

VI. Important Reminder
The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References

19. Auerbach SR, Richmond ME, Chen JM et al. Multiple risk factors before pediatric cardiac transplantation are associated with increased graft loss. Pediatr Cardiol 2011 [Epub ahead of print].