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REVIEW ARTICLE

# Pediatric heart transplantation: demographics, outcomes, and anesthetic implications*

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*Useful Data Sources
ISHLT: International Society for Heart and Lung Transplantation: http://www.ishlt.org.
PHTS: Pediatric Heart Transplant Study Group: http://www.uab.edu/ctsresearch/phts/.
OPTN: Organ Procurement and Transplantation Network: http://www.optn.org.
UNOS: United Network for Organ Sharing: http://www.unos.org.
SRTR: Scientific Registry of Transplant Recipients: http://www.ustransplant.org.

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## Summary

The evolving demographics, outcomes, and anesthetic management of pediatric heart transplant recipients are reviewed. As survival continues to improve, an increasing number of these patients will present to our operating rooms and sedation suites. It is therefore important that all anesthesiologists, not only those specialized in cardiac anesthesia, have a basic understanding of the physiologic changes in the transplanted heart and the anesthetic implications thereof.

## Introduction

The first 'successful' pediatric heart transplant was in 1967 in an 18 -day-old baby with tricuspid atresia who survived 6 h (1). It was not until the late seventies that survival became realistic with the introduction of cyclosporine, advances in donor management, organ preservation, and recipient selection, development of the transvenous cardiac bioptome for rejection surveillance, and clarification of brain death criteria. In 1982, the International Society of Heart and Lung Transplantation (ISHLT) opened a voluntary registry for pediatric heart transplantations (<18 years); since then, >8000 children have been registered and followed. Children account for ~12.5% of cardiac transplantations, with ~450 pediatric transplants reported yearly from 80 centers (most in Europe and North America) (Figure 1) (2). This article reviews current trends and outcomes for pediatric cardiac transplantation and discusses important anesthetic implications.

## Indications and demographics

The major indications for heart transplantations in infants and children are cardiomyopathy, congenital heart disease (CHD), and re-transplantation (3,4).

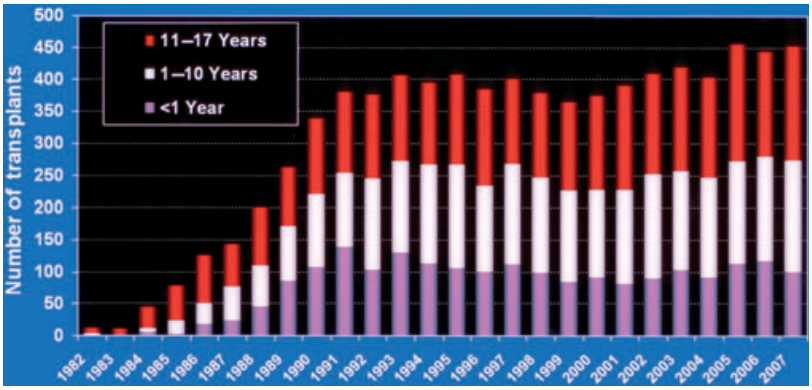


**Figure 1** Age distribution of pediatric heart recipients (by year of transplant) (2, 21).

## Cardiomyopathies (CM)

CM fall into three types: dilated, hypertrophic, and restrictive, each with different risk factors, clinical courses, outcomes, and treatment options.

*Dilated cardiomyopathy (DCM).* DCM is the most common pediatric cardiomyopathy (> 50%), accounting for 75% of transplantations for CM. It is caused by neuromuscular disorders, viral myocarditis, chemotherapeutic agents, metabolic diseases, and genetic factors (5). Treatment includes $\beta$-blockers, vasodilators, diuretics, and biventricular pacing, with most studies showing a 5-year survival rate of 40–80% (6,7); the subgroup of viral myocarditis has the best chance of recovery within the first 2 years (freedom from death or transplantation of 70% at 1 year and 50% at 5 years after the diagnosis) (8,9).

*Hypertrophic cardiomyopathy (HCM).* HCM constitutes about 25% of pediatric CM and is characterized by ventricular hypertrophy not caused by an underlying obstruction or stenosis. Seventy-five percent of cases are idiopathic, with inborn errors of metabolism (Pompe disease), malformation syndromes (Noonan, Beckwith-Wiedemann), and neuromuscular disorders (Friedreich's ataxia) also being associated with HCM (10,11). Children with inborn errors of metabolism and those with early presentation in infancy, lower shortening fraction, and higher posterior wall thickness on echocardiography are at high risk of death. Progression to a dilated or restrictive cardiomyopathy is often the indication for transplantation (12).

*Restrictive cardiomyopathy (RCM).* Restrictive cardiomyopathy (RCM), a diastolic cardiac dysfunction defined as restrictive filling with normal ventricular size and wall thickness, is rare in children (2.5–3%) (10,13). It responds poorly to medical or surgical treatment and can lead to significant pulmonary hypertension. Survival rates for 1, 5, and 10 years after diagnosis are 80%, 39%, and 20%, respectively, thus transplantation is considered early in the disease process (14–16).

## CHD

Initially, a primary indication for management of hypoplastic left heart syndrome (17), transplantation was limited by the low number of available organs for infants and high waiting list mortality. Advances in cardiac surgery and pediatric cardiology for complex CHD have significantly improved survival, resulting in a shift away from heart transplantation in infants as a primary therapeutic modality (Figure 2). Current indications are previously repaired or palliated CHD with poor ventricular function, with single ventricle lesions (especially the failing Fontan) accounting for the majority (36%) of CHD patients transplanted (17–19).

## Re-transplantation

Retransplantation is a small, but steadily growing percentage of heart transplantation (6–7%). The major indications are posttransplant coronary vasculopathy (51%) and graft failure (16%) (2). Unfortunately, survival after re-transplantation is inferior to that seen after primary transplantation (20).

The pattern of indications for pediatric heart transplantation has changed over the past 23 years. From 1988 to 1995, 78% of transplants occurred in infants for CHD (mostly hypoplastic left heart syndrome) and 16% for CM (21). More recently (1996–2008), 63% of transplantations in infants occurred for CHD and 31% for CM. In older children, cardiomyopathy is the major indication (64%), with CHD accounting for 24% and re-transplantation 7% (21). North America has the highest proportion of infant heart transplantations (27%) compared to the rest of the world (11%) (2).

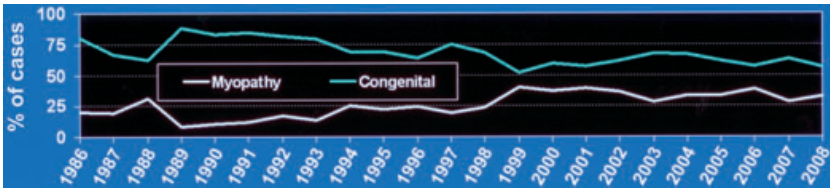


**Figure 2** Diagnosis in pediatric heart recipients (age <1 year) (2, 21).

## Contraindications

In addition to general contraindications (active malignancy, uncontrolled infection, multi-organ failure, psychosocial factors), irreversible pulmonary hypertension (>6 Wood Units·m$^{-2}$) or severe organ dysfunction (cirrhosis, renal insufficiency, major neurodevelopmental disorder or stroke) can be exclusion criteria (3,4). Current controversies include indications for combined organ transplants (heart–kidney/liver/lung), controlled infections (HIV, hepatitis), or malignancies (22–24).

## Timing of transplantation and waiting list mortality

Generally, transplantation is considered when it offers an important survival advantage over alternative management options. According to the American Heart Association, heart transplantation is a Class 1 (Level B) recommendation for children with stage D heart failure and Class 1 (Level C) for stage C heart failure (3,25) (Table 1). The United Network for Organ Sharing (UNOS) will list these children as Status 1A or 1B in their medical urgency allocation algorithm (26) (Table 2).

As of June 11, 2010, there were 3142 patients on the US waiting list for heart transplantation, including 262 infants and children. The median waiting time for children is about 80 days, compared to 170 days for adults <65 years of age (27). Unfortunately, children have the highest waiting list mortality. An analysis of 3098 children listed for transplant in the United States between 1999 and 2006 found that 17% died while waiting, 63% were transplanted, 8% recovered, and 12% remained listed (28). Most of the children who died on the waiting list weighed <15 kg. Multivariate predictors of waiting list mortality (hazard ratio 1.9–3.1) included extracorporeal membrane oxygenation (ECMO), CHD, ventilator support, dialysis, listing status 1A, and nonwhite race/ethnicity. The level of invasive hemodynamic support was a stronger predictor of mortality at 30 days than UNOS status. For example, an infant (<10 kg) on ECMO for CHD had a 12-fold increased risk of death compared to a child >10 kg with cardiomyopathy on inotropic support, although both would be listed as UNOS 1A. This study highlighted a major problem of the current organ allocation system, namely the increasing conflict between medical urgency and waiting list seniority.

## Outcomes

### Survival

The average survival (time at which 50% of recipients remain alive) varies with the age of the recipient at transplant. The average survival is 18 years for infants, 15 years for children aged 1–10 years, and 11 years for teenagers (Figure 3) (2). The highest risk of dying is within the first 6 months and is mainly caused by acute rejection or infection. Risk factors for 1-year mortality include the degree of pretransplant support (ECMO, ventilator, dialysis), a diagnosis of CHD, re-transplantation, severe infections, panel reactive antibodies ≥10%, increased donor age, and earlier era of transplant. Inotropic support, hos-

**Table 1** Heart failure staging in children. Modified from (25)

| Stage | Interpretation | Clinical Examples |
|---|---|---|
| A | At risk of developing heart failure | Congenital heart defects<br>Family history of cardiomyopathy<br>Anthracycline exposure |
| B | Abnormal cardiac structure/function<br>No symptoms of heart failure | Univentricular hearts<br>Asymptomatic cardiomyopathy |
| C | Abnormal cardiac structure/function<br>Past or present symptoms of heart failure | Repaired or unrepaired congenital heart disease<br>Cardiomyopathies |
| D | Abnormal cardiac structure/function<br>Continuous i.v. infusion of inotropes or $PGE_1$<br>Mechanical ventilatory and/or circulatory support | Same as stage C |

**Table 2** United Network for Organ Sharing allocation algorithm for pediatric medical urgency. Modified from (26)

| | |
|---|---|
| Status 1A | I. At least one of the following devices/therapies<br>Mechanical circulatory support<br>Balloon pump<br>Mechanical ventilation<br><6 months old, PGE, or pulmonary hypertension at >50% systemic pressures<br>High-dose or multiple i.v. inotropes (Dobutamine or Dopamine >7.5 mcg·kg$^{-1}$·min$^{-1}$)<br>Unresponsive, recurrent life-threatening arrhythmias (if all thoracic organ transplant center within the organ procurement organization agree)<br>II. Heart status 1A Justification Form within 24 h of listing |
| Status 1B | At least one of the following<br>Low-dose i.v. inotropes (Dobutamine or Dopamine <7 mcg·kg$^{-1}$·min$^{-1}$)<br><6 months old, not meeting criteria as Status 1A<br>Falls of growth curve and exhibits poor systemic ventricular function, or has failed previous surgical intervention |
| Status 2 | All other actively listed children |

pitalization, previous malignancy, ischemia time, cytomegalovirus, or HLA mismatch had no effect on 1-year mortality. Survival rates have improved in the recent era, primarily because of increased survival during the first 6 months. Preliminary data suggest a 30% improvement in the risk-adjusted 5-year survival rate. On the other hand, media and long-term outcomes have not been significantly affected by advances in posttransplant care. Centers with higher pediatric transplant volume generally have better survival rates (2).

## Causes of death

Nearly 50% of deaths within 30 days are caused by graft failure (primary or secondary to rejection) and technical factors. Acute rejection, infection, and multiple organ failure each account for about 10%. During the first 3 years, acute rejection is the leading cause of death, whereas after this period almost 60% of deaths are attributable to coronary allograft vasculopathy (CAV) or graft failure (2).

## Transplant morbidity

With improving survival, the focus of posttransplant care is shifting toward transplant morbidity (2).

*Functional status*. There are only limited data available for children who have survived at least 10 years after transplantation; 92% are reported to have no limitations on physical activity, and 1% requires total assistance. Growth rate is normal in the majority of transplant recipients. Up to a quarter of patients may have difficulties with emotional adjustment.

*Rehospitalization*. Within the first year, 50% of children need to be hospitalized: 35% for infection, 25% for rejection, and 15% for both. By 10 years, this number drops to about 25% (infections [36%], rejection [15%], or both [4%]) and is similar to adult data (2).

*Rejection*. Rejection is one of the major complications and remains an ever present threat. Approximately 30–

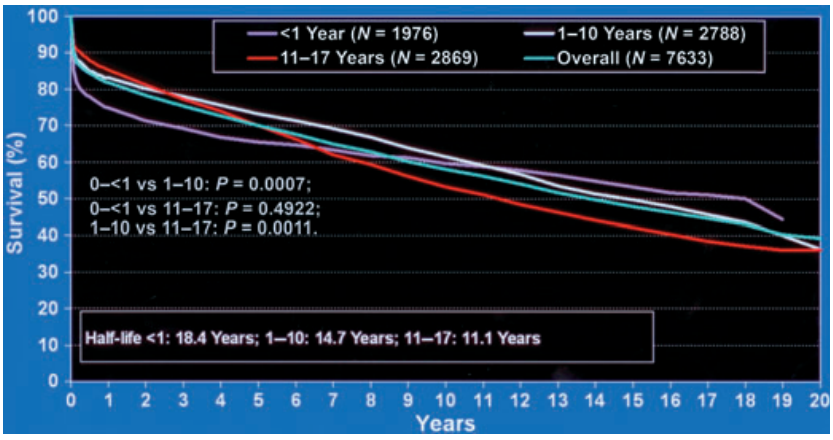


**Figure 3** Kaplan Meier survival by era for transplants from January 1982 through June 2007. (Half life: average survival, the time at which 50% of recipients remain alive.) Modified from (2, 21).

35% of children experience at least one episode of acute rejection within the first year, despite the increasing use of induction agents. The incidence begins to decline after 3 years, reaching about 12% between 5 and 10 years. Of note, adolescents are notorious for low compliance (up to 20%) with antirejection regimens. Rejection is not only one of the major causes of death, but it is also associated with the development of cardiac allograft vasculopathy and therefore graft survival (29,30).

Recipient CD4 T cells recognize foreign antigen in the donor heart, triggering T-cell activation, interleukin-2 (IL-2) secretion, and activation of monocytes/macrophages, B cells, and cytotoxic CD8 cells. Prevention and ongoing suppression of such activation is the fundamental concept behind immunosuppressive therapy. The majority of centers use an induction phase followed by a maintenance regimen.

The *induction phase* is purported to reduce the incidence of early rejection and possibly delay or avoid treatment with nephrotoxic agents. This is generally achieved by the depletion of the T-cell pool with monoclonal or polyclonal antibodies or prevention of IL-2 secretion with specific IL-2 receptor antagonists. Compared with classical agents like cyclosporine, renal dysfunction is less likely with these agents. Induction agents include the following: (i) *OKT3* is a murine monoclonal antibody directed against CD3 molecules on T cells; (ii) *Rabbit or equine antithymocyte globulin* (ATG) are polyclonal IgG antibodies extracted from thymocytes; (iii) *Basiliximab and daclizumab*, in contrast to OKT3 and ATG, are specific IL-2 receptor antibodies that are usually well tolerated and increasingly being used; currently, 22% of pediatric heart transplant recipients are treated with these specific IL-2 receptor antibodies. The most recent ISHLT registry reports that 60% of pediatric cardiac recipients received an induction therapy in 2008, a significant increase from 37% in 2001. Nevertheless, the incidence of rejection episodes between discharge and 1 year has not decreased, nor has the choice of induction agents influenced survival (2).

Several classes of drugs are currently used for *maintenance* immunosuppression, including corticosteroids, calcineurin inhibitors (cyclosporine, tacrolimus/FK-506), antiproliferative agents (azathioprine, mycophenolate mofetil [MMF]), and target of rapamycin inhibitors (sirolimus) (31). *Corticosteroids* are nonspecific antiinflammatory agents, but because of their deleterious side effects, especially on growth and glucose metabolism, most transplant centers try to restrict or avoid their use for routine immunosuppression. *Cyclosporine* and *tacrolimus* (*FK506*) inhibit the transcription of the IL-2 gene, thereby reducing the production of IL-2. Cyclosporine therapy is often complicated by hypertension, nephrotoxicity, neurotoxicity, liver dysfunction, hyperlipidemia, hypertrichosis, gingival hyperplasia, and posttransplant lymphoproliferative disease (PTLD). Tacrolimus (FK506) has a slightly different side-effect profile than cyclosporine (higher incidence of diabetes and neurotoxicity with similar nephrotoxicity) and might be more effective. Consequently, it is increasingly replacing cyclosporine in many protocols (32–34). Antiproliferative agents inhibit B- and T-cell proliferation; MMF is replacing azathioprine in many centers because of less bone marrow suppression and nephrotoxicity. Sirolimus, because of its adverse effects on wound healing, bone marrow function, and triglyceride levels, has mainly been used for rejection therapy. This might change in the future because adult studies suggest that sirolimus may reduce the progression of coronary vasculopathy (35).

Many pediatric centers use a combination of triple immunosuppression therapy for maintenance for the first year: 38% received cyclosporine, 58% tacrolimus, 20% azathioprine, 59% MMF, 55% prednisone, and 8% sirolimus. Between years 1 and 5 after transplant, there is a trend toward reducing the number of agents, early steroid withdrawal, and reduced use of cyclosporine and azothioprine in favor of tacrolimus and MMF (2).

*Rejection surveillance*. Despite induction therapy, the first-year rejection rate (30–35%) has not decreased (2). The diagnosis of rejection is made on clinical signs, echocardiographic evidence of ventricular dysfunction, and endomyocardial biopsy (36). Rejection episodes can be classified into acute vs chronic, cellular vs antibody mediated, and with or without hemodynamic compromise (31). Rejection with hemodynamic compromise seems to occur twice as often in children: 11% compared to 5% in adults (37,38). Treatment strategies for rejection episodes are based upon the etiology and severity, and usually include a 3-day pulse with steroids or ATG, and if antibody-mediated rejection, the addition of i.v. immunoglobulin, plasmapheresis, or both. Bortizemab, a proteasome inhibitor directly targeting the antibody-producing plasma cells, is the newest addition to the antirejection armamentarium and currently undergoing investigation (39–42). For children, rejection surveillance with serial endomyocardial biopsies is complicated by patient size, difficult vascular access, and the need for anesthesia or deep sedation. The timing of biopsies is tailored to the probability of rejection; the first is usually obtained 7–14 days after transplant, and further biopsies are performed at 4-, 6-, 9-, and 12-week posttransplant, then

at 6 and 9 months. After the first year, most centers continue surveillance with 6 monthly biopsies and annual coronary angiography. In the near future, gene expression profiling of peripheral blood specimens will reduce the need for frequent endomyocardial biopsies (43,44).

*Cardiac allograft vasculopathy*. At 10 years, 34% of children have CAV (2), with the onset of CAV influenced by age at transplantation. Freedom from CAV 8-year posttransplant is higher in infants and younger children (71% and 74%, respectively) than in children >11 years (56%). Once CAV occurs, the 3-year graft survival is 45% for all pediatric age groups. As adults have a 50% graft loss at 9 years after CAV diagnosis, it is uncertain whether CAV causes a more aggressive rate of graft deterioration in younger patients or whether CAV is diagnosed earlier in adults as a result of more aggressive surveillance (45). It is also unclear why short ischemic times (<2 h) increase the incidence of CAV in children younger but not older than 10 years.

*Renal dysfunction*. Ten years after transplant, 11% of children and adolescents compared with 60% of adults have severe renal dysfunction (dialysis, kidney transplant, serum creatinine $>2.5$ mg·dl$^{-1}$).

*Malignancy*. Eight percent of children develop malignancies at 10 years after transplant in contrast to 32% of adults. Almost all pediatric malignancies are lymphomas in contrast to the skin or nonlymphoma tumors seen in adults.

*Hypertension*. Eight years after transplantation, 69% of pediatric survivors had hypertension, compared to 94% of adults at 5 years.

## New developments

ABO-incompatible transplantation in infants, donation after cardiac death, and the increasing number of single ventricle patients with a failed Fontan palliation represent some of the latest developments in pediatric cardiac transplantation.

### ABO-incompatible heart transplantation in infants

A shortage of donor organs, especially for infants, and the high waiting list mortality have triggered the search for new concepts to enlarge the available donor pool (46). In the adult population, ABO-incompatible solid organ transplantations are absolutely contraindicated because of hyperacute rejection mediated by preformed antibodies. However, the immature immune system of newborns does not produce isohemagglutinins and levels remain low until 12–14 months of age; in addition, the complement system is not fully competent in young infants. As a result, infants can be recipients of ABO-mismatched organs. This concept has been successfully used over the last decade, and the existing data suggest that outcomes are similar to matched recipients as long as important criteria and strategies are followed: the ABO-mismatched organ recipient must be <15 months of age, have low or no isohemagglutinins levels, and fulfill all other transplant criteria (46,47). During the pretransplant phase, they should only receive ABO-compatible blood products and never any whole blood. At the onset of cardiopulmonary bypass, recipients typically receive a two times blood volume exchange transfusion, which can be repeated several times depending on the level of isohemagglutinins checked periodically during surgery and in the postoperative period. The removed red blood cells can be 'washed' in a cell saver and retransfused.

### Donation after cardiac death

The concept of donation after cardiac death or transplantation after declaration of cardiocirculatory death (DCD) was reintroduced in the late nineties. With the consent of the family, nonbrain-dead children with a terminal diagnosis (e.g. severe cerebral hemorrhage) are taken to the operating room, prepared for organ retrieval, and support is withdrawn by the primary care or critical care physician. Death is declared after cardiopulmonary arrest, and there is an additional waiting period of several minutes before organs are harvested. Concerns about myocardial hypoxic-ischemic injury during the prearrest time initially discouraged the harvesting of hearts, but evidence suggests a 'safe' hypoxic-ischemic time of up to 30 min (48). Despite ongoing ethical and medical controversies, the first experiences with DCD in the pediatric population have been encouraging (49). One report compared outcomes of three DCD infant cardiac transplantations with 17 infants with conventional donation after brain death (50). The 6 -month survival rate was 100% in the DCD group and 84% in the conventional group; there was no difference in the number of rejection episodes or echocardiographic indicators of ventricular dysfunction.

### Failed Fontan

Children with single ventricle hearts and failed Fontan palliation represent the largest and fastest growing

group of transplant candidates with CHD (51). Indications include severe ventricular dysfunction, atrioventricular valve regurgitation, pulmonary hypertension, or long-term complications of Fontan physiology such as protein-losing enteropathy, plastic bronchitis, intractable arrhythmias, thromboembolism, hepatic and renal dysfunction, ascites, and pleural effusions. These children (and adults) have had numerous hospitalizations and are often in poor physical and mental condition; they are 'high-risk' transplant candidates and require thorough preoperative evaluation. The risk of bleeding is markedly increased because of underlying coagulopathies, multiple previous surgeries, the presence of aortopulmonary collaterals, and the need for pulmonary artery reconstruction. Malnourishment and electrolyte imbalances can aggravate preexisting arrhythmias and predispose to poor wound healing and infection. Adequate nutritional support and advanced imaging studies, including cardiac catheterization with liver biopsy and coil occlusion of collaterals, are important aspects of pretransplant management (52). A retrospective multi-institutional review of pediatric Fontan patients listed for cardiac transplantation between 1993 and 2001 reported the survival rate on the waiting list as 78% at 6 months and 74% at 12 months, which is comparable to other transplant candidates (19). Eighty percent of deaths on the waiting list occurred within the first 6 months of listing, with risk factors being ventilatory support, UNOS status 1, age $<4$ years, and shorter interval since the Fontan procedure ($<6$ months). The actual survival rates after transplantation were 77% at 1 year, slightly less but not significantly different from data for other recipients [Non-CHD (91%) or other CHD indications (85%)]. Interestingly, protein-losing enteropathy resolved in all children who survived 30 days. There are also reports from individual institutions (53).

## Physiology of the transplanted heart

After transplantation, the function of the surgically denervated heart is dependent on an intact Frank Starling mechanism (ability of the myocardium to increase contractility and hence stroke volume in response to stretch (preload)) and stimulation from endogenous circulating catecholamines. The transplanted heart is characterized by elevated filling pressures, increased end-diastolic and end-systolic volumes, low normal left ventricular ejection fraction, and a restrictive physiology (diastolic dysfunction). The left ventricular end-diastolic pressure is typically around 12 mmHg 4–8 weeks after transplantation. Afferent and efferent denervation have multiple effects on circulatory control mechanisms, including altered cardiovascular responses to exercise, cardiac electrophysiology, and responses to cardiac pharmacologic agents (Table 3) (54). Exercise testing demonstrates that transplanted children can usually achieve only 60–70% of normal capacity. Exercise generates an increase in cardiac output by increases in stroke volume, a highly preload-dependent process, with tachycardia occurring only later in response to circulating catecholamines; the peak heart rate achieved is lower than normal. There are several case reports of profound bradycardia and even cardiac arrest after administration of neostigmine for reversal of neuromuscular blockade (55–59). The denervated heart is extremely sensitive to adenosine, with the magnitude and duration of effect on the AV node being three to five times greater; the dose should be reduced by 50%. The lack of reflex tachycardia can lead to profound hypotension with direct vasodilators (nitroglycerine, nitroprusside, hydralazine). The incidence, timing, and extent of sympathetic reinnervation are still being investigated, but positive effects on cardiac performance during exercise have been demonstrated (60).

**Table 3** Physiology of the transplanted heart. Modified from (54)

| |
|---|
| Elevated filling pressures |
| Low normal left ventricular ejection fraction |
| Restrictive physiology (stiff heart) |
| Increased afterload (hypertension) |
| Afferent denervation |
| Silent ischemia |
| Altered cardiac baro-and mechanoreceptors |
| Less stress-induced increase in systemic vascular resistance |
| Increased blood volume (decreased natriuresis and diuresis) |
| Efferent denervation |
| Resting tachycardia (loss of vagal tone) |
| Impaired chronotropic response to stress (dependent on circulating catecholamines) |
| Electrophysiology |
| Sinus node dysfunction in immediate postoperative period |
| Normal AV node conduction |
| Shift from $\beta 1$ to $\beta 2$ receptors |
| Altered response to medications |
| No heart rate response to atropine or glycopyrrolate |
| Decreased response to digitalis; possible severe bradycardia /cardiac arrest with neostigmine |
| Exacerbated response to $Ca^{++}$channel blockers, $\beta$-blockers, adenosine |
| Exacerbated response to direct acting sympathomimetic agents |
| Decreased response to indirect acting agents (dopamine, ephedrine) |
| Possible sympathetic reinnervation |
| Enhanced contractile response and exercise tolerance |
| Higher peak heart rates during exercise |

## Anesthetic considerations for the transplanted heart

Anesthesia for patients with a transplanted heart is reviewed in detail elsewhere (61–63). The preoperative evaluation should specifically focus on cardiac function, current rejection status, presence of infections, evidence of cardiac allograft vasculopathy, status of vascular access, organ dysfunction, side effects of steroids and other immunosuppressive agents (frequently hypertension, renal dysfunction, bone marrow suppression), and psychological status. A thorough review of recent surveillance testing (echocardiography, ECG, endomyocardial biopsies, cardiac catheterizations, and coronary angiography) is essential. Any decrease in exercise tolerance or new onset of dysrhythmias should raise a high index of suspicion for rejection and/or CAV. Consultation with the patient's cardiologist as to their current status can be extremely beneficial and is therefore strongly recommended.

The anesthetic plan depends on the patient's physical status and the nature of the procedure. The importance of adequate preload, slower adaptive responses (denervation and dependency on circulating catecholamines), reduced inotropic and chronotropic reserve, and altered responses to cardiac pharmacologic agents is discussed earlier. Use of hemodynamic responses to noxious stimuli to assess adequacy of depth of anesthesia is limited.

Many anesthesia techniques have been successfully used for children with transplanted hearts. Adequate hydration and appropriate drug selection are important to avoid hypotension. Hypotension is best managed with a fluid bolus and a direct-acting sympathomimetic, if necessary, while maintaining an adequate depth of anesthesia. The increased risk of infection requires strict attention to aseptic techniques and appropriate antibiotic coverage. For the same reasons, the oral route is preferred to the nasal for endotracheal intubation. A careful risk/benefit analysis must precede the use of invasive monitoring. When planning central venous access and pressure monitoring, it should be remembered that endomyocardial biopsies are typically performed via the femoral vessels in infants and young children, and via the right internal jugular vein in older children and adults. Consideration should be given to preserving these sites for later use, if possible.

Maintenance of adequate immunosuppression in the perioperative period is essential. Postoperative gastric dysfunction can delay or impair the absorption of cyclosporine and tacrolimus, and many medications used in the perioperative period can affect immunosuppressive drug levels. Close monitoring and frequent dose adjustments are often required and should be carried out in consultation with the transplant cardiology team.

## Anesthesia for pediatric cardiac transplantation

Anesthesia can be quite challenging, depending on the indication for transplant and the age and clinical status of the child. Children with CM can present in critical condition on inotropic support and pulmonary vasodilators (milrinone, dobutamine) or with a ventricular assist device being used as a bridge to transplant. Children with previously repaired or palliated CHD are frequently underweight, malnourished, and anemic from longstanding low cardiac output, feeding problems, or protein-losing enteropathy (failing Fontan) (51–53). They are often very scared and in our experience very tolerant to sedatives and analgesics. Vascular access (arterial and/or venous) can be limited as the radial arteries may be occluded from previous use and the femoral arteries and veins from previous cardiac catheterizations and surgical access. A thorough preoperative assessment and discussion with the surgical team to specify potential alternative sites for central venous and arterial monitoring as well as peripheral bypass cannulation are essential to avoid surprises and confusion in the operating room. The potential for massive bleeding is significant as a result of scarring and adhesions from multiple previous surgeries, collateral vessels, and preexisting coagulopathy; this can prolong the dissection phase. Close coordination with the donor retrieval team is important to minimize the ischemic time for the donor organ. In addition, many children are sensitized from previous blood transfusions and may require exchange transfusions or plasmapharesis just prior to surgery. Standard anesthetic techniques for cardiac surgery are employed. As failure of the donor right ventricle postcardiopulmonary bypass is not unusual, attention needs to be focused on lowering the pulmonary vascular resistance and inotropic support (dopamine, epinephrine, milrinone) of ventricular function (64). Nitric oxide is a useful adjunct, and occasionally placing the patient on ECMO to allow for myocardial recovery and normalization of pulmonary artery pressures and resistance is necessary in the setting of actual or impending right ventricular failure.

Children presenting for re-transplantation are a combination of all these challenges (poor cardiac function from acute or chronic rejection, history of multiple previous surgeries, sensitization, etc.) plus the altered physiology of the transplanted heart and the

side effects of the immunosuppressive therapy on various organ systems.

## Summary

Recent advances in donor allocation, critical care management, and immunosuppressive therapy have led to increased survival after pediatric cardiac transplantations: The 50% survival rate for infants is currently 18 years and will most likely continue to improve. In the pediatric population, the indications for heart transplantations have slightly shifted over the years: away from 'irreparable' congenital heart defects in infants toward CM and increasingly to 'failed' repairs or palliations in older children or adolescents. Unfortunately, the mortality on the waiting list is still very high: ~20%, emphasizing the need for further changes in the organ allocation and new 'bridging' solutions like ventricular assist devices. Finally, improving transplant morbidity by finding the perfect balance between effective immunosuppression and acceptable long-term side effects will be the major challenge for the coming years.

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