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Heart transplantation

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The past four decades have seen remarkable improvements in the medical and surgical treatment of end-stage heart disease, including cardiac transplantation. Advances in surgical techniques, immunosuppression and medical management have improved transplant survival with each passing year. Improved outcomes and experience have resulted in expanded eligibility for transplantation. Advancements in assist devices and the medical management of heart failure have resulted in an increased need for organs as more patients survive to need transplantation. Consequently, over the last 20 years of the previous century (Figure 8.1), there was a rapid increase in the number of transplantations performed worldwide. However, the advent of other technologies and societal changes has resulted in fewer suitable cardiac donors and correspondingly declining numbers of transplantations performed in the past 10 years. This has occurred despite a better understanding of donor suitability that has allowed the use of donors that would have never been considered appropriate a few years ago.

According to the International Society for Heart and Lung Transplantation (ISHLT) Registry, from January 1, 2004 to June 20, 2006, both adult heart transplant recipients and donors have gradually increased in age, with the average recipient age being 50.7 ± 12.5 years and donor age 38.5 ± 13.0 years. The majority of heart transplant recipients are male (77.1% in the most recent ISHLT Registry report).

Survival after cardiac transplantation has progressively improved (Figure 8.2). Risk factors for mortality within the first year include temporary circulatory

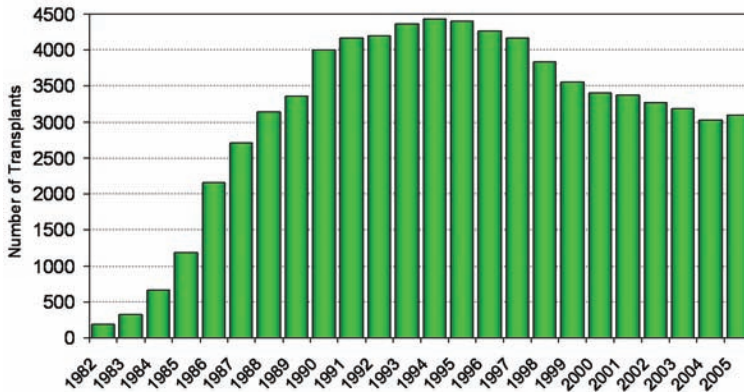
support pretransplant, a pretransplant diagnosis of congenital heart disease, the use of a ventricular assist device pretransplant, recipient history of diabetes mellitus, ventilator support pretransplant, dialysis pretransplant, cerebrovascular event pretransplant, recipient previous pregnancy, recipient with infection requiring IV antibiotics within 2 weeks pretransplant, long-term pulsatile device support pretransplant, recipient prior sternotomy, and donor cytomegalovirus (CMV) +/-recipient CMV-status. Continuous variables that increase mortality in the first year include recipient age, recipient weight, donor age, ischemic time, center volume (inverse relationship to survival), recipient pretransplant pulmonary artery systolic pressure and pulmonary vascular resistance, recipient pretransplant bilirubin, and recipient pretransplant creatinine. Risk factors for mortality within 5 years following transplantation, conditional on survival to 1 year, include re-transplantation, cardiac allograft vasculopathy within the first year, ventilator at time of transplant, diabetes mellitus, treatment for rejection prior to discharge, treatment for infection prior to transplant discharge, rejection between discharge and first year, total HLA mismatches (0-4 vs 5-6), panel reactive antibody (PRA) >10%, other surgical procedures (excluding cardiac reoperation) prior to transplant discharge, and diagnosis of ischemic heart disease vs. cardiomyopathy. Continuous risk factors for mortality at 5 years include recipient age, donor age, and donor/recipient body mass index ratio (inverse relationship).

Early mortality after transplantation often relates to the severity of illness in the recipient. Therefore, transplantation is a balance between the increased mortality risk of transplanting sicker patients and the improved survival seen in this cohort. Conversely,

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NUMBER OF HEART TRANSPLANTS REPORTED BY YEAR

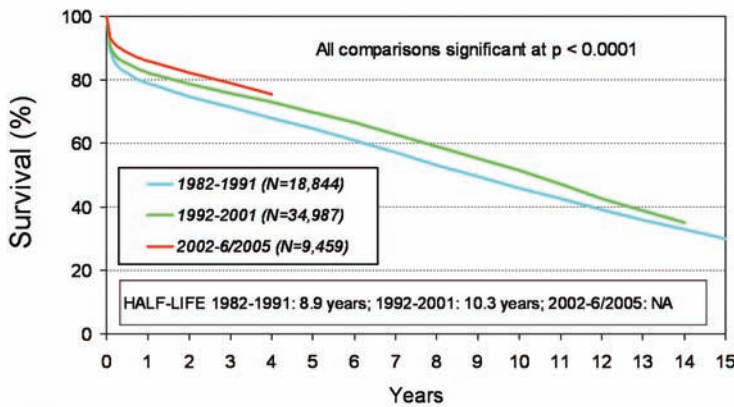


ISHLT 2007
 J Heart Lung Transplant 2007;26: 769-781

Figure 8.1 Number of heart transplantations performed annually worldwide as reported to the Registry of the International Society for Heart and Lung Transplantation. (Reprinted with permission from Taylor DO, Edwards LB, Boucek MM, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult heart transplant report – 2007. *J Heart Lung Transplant* 2007;26:769–81.)

ADULT HEART TRANSPLANTATION

Kaplan-Meier Survival by Era (Transplants: 1/1982 – 6/2005)



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Figure 8.2 Heart transplant survival by era. (Reprinted with permission from Taylor DO, Edwards LB, Boucek MM, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-second official adult heart transplant report – 2007. *J Heart Lung Transplant* 2007;26:769–81.)

with the improvement in medical management of heart failure, the survival advantage of transplanting status 2 (see status descriptions later in this chapter) patients has been questioned. This is important because, in the USA in 2004, 36% of patients were status 1A at transplantation, 36% were status 1B, and 28% were status 2. Status 2 patients still accrue a survival advantage from transplantation, although

it may take at least 2 years before this survival benefit becomes evident.

Recipient selection

The pretransplant evaluation of a potential recipient (Table 8.1) must not only determine whether the cardiac disease is significant enough to warrant trans-

Table 8.1 Evaluation for heart transplantation

Complete history and physical examination
Chest radiogram
EKG
Echocardiogram
Coronary angiogram
Cardiopulmonary exercise test
Right heart catheterization (with vasodilator challenge when indicated)
Screening laboratory studies (chemistry, hematology, coagulation, endocrine, blood type, lipid panel, HbA1c in patients with diabetes, PSA in males)
Serologic studies (hepatitis A, B, and C; HIV, CMV, EBV, <i>Toxoplasma</i> spp., VDRL, varicella)
PPD and anergy testing
Urinalysis
24-hour urine collection (creatinine clearance, protein)
Pulmonary function testing
Carotid artery Doppler study
Lower extremity ankle–brachial indices
Dental radiogram and examination
Ophthalmologic consultation (if has diabetes or aged >50 years)
Abdominal ultrasound examination
Colonoscopy (age ≥50)
Panel-reactive antibody screen
HLA typing
Social work consult
Nutrition consult
Gynecologic exam in females
Mammogram in females aged >40 years
Chest CT if patient aged >40 years, has smoking history, or has had previous chest surgical procedure

CMV, cytomegalovirus; CT, computed tomography; EBV, Epstein–Barr virus; HbA1c, glycated hemoglobin; PPD, purified protein derivative; PSA, prostate-specific antigen; VDRL, Venereal Disease Reference Laboratory.

plantation, but also define the presence of other medical conditions that might compromise outcome after transplantation. Abnormalities discovered on screening should be evaluated definitively before listing, although the presence of severe heart failure can often render it difficult to distinguish between primary end-organ disease and reversible organ dysfunction due to low cardiac output and/or increased venous pressure. This dilemma is particularly manifest in organs such as the kidney and lung, the functions of which reflect perturbations in hemodynamics. In some cases, biopsy may be required to discriminate between reversible dysfunction related to heart failure and permanent parenchymal damage.

Evaluation for heart transplantation revolves around establishment of a survival benefit of transplantation over optimized medical and non-transplant surgical therapies. The current 1-year survival rate after heart transplantation is over 80%, so transplant candidates should be expected to have a worse survival with other surgical or medical options. An in-depth heart failure cardiology evaluation is indicated before consideration for transplantation. Until the patient has failed optimal conventional medical and surgical management, consideration for heart transplantation should remain secondary. The most common reason for referral for heart transplant evaluation is left ventricular systolic dysfunction (regardless of etiology), although patients with angina refractory to maximal medical therapy, life-threatening arrhythmias, right ventricular failure, hypertrophic cardiomyopathy, etc. may also benefit from transplantation. The evaluation must be individualized, because prognostic characteristics vary with the underlying pathology.

Conventional therapy encompasses treatment of underlying myocardial ischemia, valvular dysfunction, arrhythmias, and conduction disorders. Medical therapy should be optimized (addressing neurohumoral and hemodynamic variables), circulatory consequences of other medical conditions (i.e. thyroid disease, anemia) treated, and patient behaviors that adversely affect the heart failure syndrome corrected. In some cases, the full benefit of interventions (i.e., revascularization of ischemic myocardium, β -blocker therapy, and resynchronization therapy) may be delayed and ample time must be allowed to demonstrate their benefits before deciding whether an individual is a candidate for transplantation.

Key points 8.1 If the patient's condition permits it, heart failure should be optimally treated before evaluation and listing for heart transplantation. Optimal therapy includes:

Treatment of myocardial ischemia by percutaneous or surgical revascularization, if indicated and possible

Treatment of valvular heart disease surgically if appropriate

Optimized medical therapy including:

- Angiotensin-converting enzyme (ACE) inhibitor (or angiotensin receptor blocker [ARB])
- β Blocker
- Aldosterone antagonist
- Hydralazine and nitrates (if intolerant of ACE inhibitors and [ARBs])
- Diuretics (as indicated by volume status)

Prevention of sudden death by implantation of implantable cardioverter–defibrillator

Restoration of sinus rhythm in patients with atrial fibrillation or atrial flutter, if possible

Resynchronization therapy in patients with left ventricular dyssynchrony

Optimal treatment of non-cardiac diseases that adversely affect cardiac performance (i.e., thyroid disease, anemia)

Confirmed abstinence from alcohol, smoking, and recreational drug use

Intensive education and counseling in patients with a history of non-compliance

An important component of the transplant evaluation is the assessment of the patient's risk of mortality associated with medical or non-transplant surgical treatment options. This includes an assessment of functional capacity based on cardiopulmonary exercise testing (typically expressed as peak exercise oxygen consumption or $VO_{2\max}$), the presence of ventricular arrhythmias, measurement of neurohormonal factors (e.g., plasma levels of brain natriuretic peptide and norepinephrine), estimation of ejection fraction, and assessment of the New York Heart Association (NYHA) functional class. Frequently, a consensus prognosis can be estimated. However, many patients exhibit conflicting profiles, with certain parameters suggesting an ominous prognosis whereas others are more reassuring. Reconciling disparate findings is

challenging and may mandate additional assessment and/or observation. Some transplant programs calculate a heart failure survival score (as described by Aaronson and Mancini) that incorporates $VO_{2\max}$, left ventricular ejection fraction, serum sodium, QRS duration, presence or absence of coronary artery disease, and heart rate to stratify patient mortality risk. Patients defined as high risk by the heart failure survival score are considered for listing if they do not have other contraindications to transplantation.

Key points 8.2 The typical profile of a patient listed for heart transplant (as assessed after optimization of heart failure therapy)

Functional classes IIIB–IV

Left ventricular ejection fraction <30%

Cardiac index <2.5L/min per m^2 (in a euvoletic state)

Peak exercise oxygen consumption <14 mL/kg per min (or even lower in patients clinically stable on β -blocker therapy)

Plasma brain natriuretic peptide level >500 pg/mL

The timing of listing for heart transplantation has been altered by two recent advances:

1. The routine implementation of implantable cardioverter–defibrillators (ICDs) for primary prevention of sudden death
2. The use of mechanical circulatory support devices to support patients as a “bridge” to heart transplantation.

Both technologies allow clinicians a greater margin of safety when dealing with patients whose mortality risk was underestimated, because they allow for the possibility of “rescue to transplant” interventions.

Sudden cardiac death contributes substantially to mortality of patients with heart failure. Although there is a paucity of data in patients with advanced disease, ICDs have been shown to reduce mortality in patients with mild-to-moderate heart failure. In addition, cardiac resynchronization therapy (biventricular pacing) has been shown to improve the functional status and survival of patients with left ventricular systolic dysfunction and dyssynchronous contraction. With further refinement of these therapies, conven-

tional assessments of pretransplant and heart failure mortality will need to be revisited to better determine optimal listing time for heart transplant.

Patients are also screened for conditions that affect perioperative mortality after transplantation. Recent pulmonary embolism, active peptic ulcer disease, smoking or alcohol abuse within 6 months, and active infection are examples of conditions that might preclude transplantation at the time of assessment, but may not be absolute contraindications to transplantation. Other conditions such as multiple prior mediastinal operations, chest wall radiation, or limited venous access must be considered on an individual basis.

In addition, the non-cardiac evaluation for heart transplantation identifies conditions that impact prognosis independent of cardiac status and complicate post-transplant management or compromise outcome. Although the contraindications to heart transplantation (Table 8.2) have evolved to allow consideration of transplantation of increasingly compromised patients, the limited donor supply suggests that centers remain mindful of individual long-term survival and other patients on the transplant wait list. The decision not to list a patient is typically due to multiple coexistent contraindications. Even so, occasionally, combined solid organ transplants (i.e., heart–kidney, heart–liver, heart–lung) can address complicating conditions previously considered preclusive of heart transplant.

Case: recipient selection

A 56-year-old man developed severe left ventricular dysfunction after a myocardial infarction 7 years ago, but with appropriate management with an angiotensin-converting enzyme (ACE inhibitor and a β blocker he had remained functional class II. Six months ago, despite no new clinical events, his symptoms progressed to functional class III. Coronary angiography revealed an occluded left anterior descending artery (LAD) but MRI revealed an infarcted anterior wall. His EKG revealed a QRS duration of 150ms, so he underwent biventricular pacer/AICD (automatic implantable cardioverter defibrillator) implantation. He was also started on spironolactone. His condition improved for 1–2 months, but over the last few months he has been hospitalized three times for heart failure, despite compliance with his dietary regimen and increasing diuretic therapy. His BNP at his last hospital discharge was 1200 and on

Table 8.2 Possible contraindications to heart transplantation

Condition	Outcomes of concern
Age >65 years	Decreased survival benefit
Primary renal insufficiency	Decreased survival, accelerated progression
Hepatic insufficiency	Decreased survival, abnormal pharmacokinetics
Active peptic ulcer disease	Exacerbation with corticosteroids
Chronic inflammatory bowel disease	Increased infectious risk
Pulmonary vascular disease	Right ventricular failure, decreased survival
Chronic lung disease	Decreased survival, functional limitation, infectious risk
Peripheral vascular disease	Functional limitation, accelerated progression, infectious risk
Stroke (recent)	Hemorrhagic transformation
Pulmonary embolism (recent)	Hemorrhagic transformation, infection
Malignancy	Premature mortality, accelerated progression with immunosuppression
Infection	Spread with immunosuppression
Diabetes mellitus	Premature mortality, end-organ compromise
Amyloid	End-organ compromise, allograft recurrence
Sarcoid	End-organ compromise, allograft recurrence
Obesity	Decreased survival benefit
Medical non-compliance	Inadequate follow-up care, decreased survival
Smoking	Infectious risk, accelerated pulmonary and vascular disease

cardiopulmonary exercise testing his $VO_{2\max}$ was 9.8 mL/kg per min with a respiratory exchange ratio of 1.15. Transplant evaluation revealed no contraindications to transplantation and the patient was placed on the waiting list.

The waiting list

Once a patient is designated a heart transplant candidate by a program approved by the United Network for Organ Sharing (UNOS), the patient's name is entered on the UNOS heart waiting list with the prospective recipient's ABO blood type and center-established acceptable donor weight range. The patient's transplant priority must also be indicated, using the UNOS priority system (Table 8.3). Donor hearts are allocated based on ABO type, weight range compatibility, acuity, and accumulated waiting time at the designated status for recipients within the local organ procurement organization (OPO). If no local recipients are identified, the organ is offered regionally and then nationally, again discriminating between potential recipients based on ABO type, weight range, status, and time at status. Waiting time depends on a number of factors, including priority status, body size, ABO type, region, and recipient sensitization. As a result of the shortage of donor organs, the interval between listing and transplantation may be long.

When a patient's acuity of illness does not conform to the designated criteria, the transplant center may petition to list the individual at a higher priority that more accurately reflects disease acuity. Examples would include patients with recurrent life-threatening arrhythmias or refractory myocardial ischemia. Such a request is forwarded to a regional review board representing other transplant centers in the region. If the review board agrees, the patient's status is upgraded. At the time of writing, centers may list the patient at the higher status pending the review, but are then subject to review and/or disciplinary action if the review board finds insufficient evidence to justify the higher listing status.

Heart failure management seeks to maximize survival and quality of life, although survival takes precedence for a listed patient. Interventions that may improve quality of life at the expense of mortality risk should be avoided if possible, e.g., the use of outpatient inotropic therapy should be minimized, particu-

Table 8.3 Heart transplant candidate listing status

UNOS waiting list status (in order of priority)	Patient/Management description
1A	(a) Mechanical circulatory support ^a (excepting LVAD or RVAD) ^b (b) Mechanical circulatory support (including LVAD or RVAD) with complications (c) Continuous mechanical ventilation (d) Continuous infusion of high dose intravenous inotropic agent ^c with continuous invasive hemodynamic monitoring
1B	(a) RVAD and/or LVAD, uncomplicated (b) Continuous infusion of intravenous inotropic agent
2	Patients actively awaiting heart transplant not meeting criteria as 1A or 1B
7	Patients temporarily unsuitable to undergo transplantation

^aTotal artificial heart, intra-aortic balloon pump, or extracorporeal membrane oxygenator.

^bPatients with an LVAD and/or RVAD (uncomplicated) are allowed 30 days time at 1A status designated at the discretion of the transplant center.

^cDobutamine $\geq 7.5 \mu\text{g}/\text{kg}$ per min, milrinone $\geq 0.5 \mu\text{g}/\text{kg}$ per min.

LVAD, left ventricular assist device; RVAD, right ventricular assist device.

larly in the absence of an ICD, because this approach may increase mortality. Patients refractory to oral agents and whose characteristics predict a prolonged wait until transplantation should be considered for mechanical circulatory support with a left ventricular-assist device (VAD), right VAD, or total artificial heart (Figure 8.3). Mechanical circulatory support as a "bridge to transplant" results in improved systemic perfusion and end-organ function, and allows patient rehabilitation, thus optimizing post-transplant outcome. Hospital discharge, which decreases costs

(a)

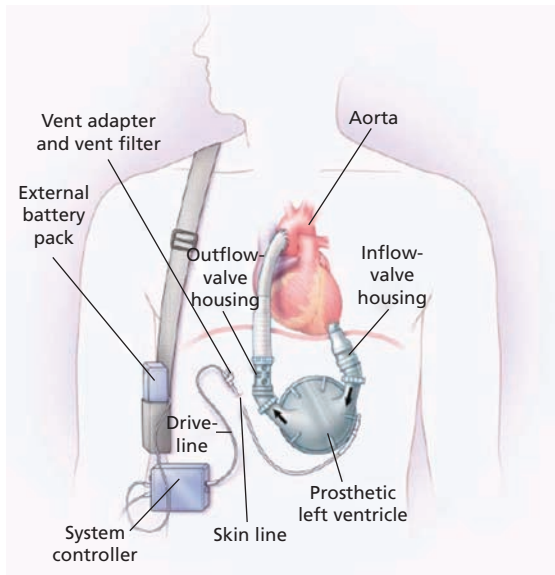
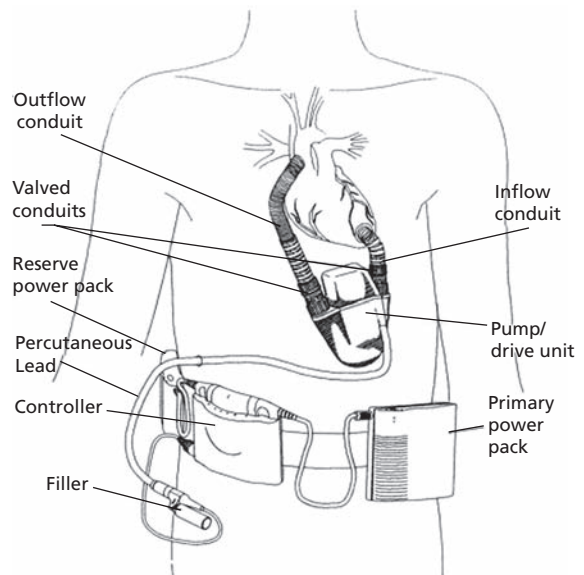


Figure 8.3 Two of the left ventricular assist devices most frequently used as a bridge to transplantation are the HeartMate vented electric device (left panel) and the Novacor left ventricular assist system (right panel). (Reprinted with permission from Rose EA, Gellins AC, Moskowitz AJ, et al. Long-term use of a left ventricular

(b)



assist device for end-stage heart failure. *N Engl J Med* 2001;345:1435–43 (left panel) and Deng MC, Loebe M, El-Banayosy A, et al. Mechanical circulatory support for advanced heart failure: effect of patient selection on outcome. *Circulation* 2001;103:231–7 (right panel).)

and encourages rehabilitation, is possible using many of these devices. This alternative must be weighed against the additional surgery and risk of sensitization. If recipient and region characteristics are predictive of a short pretransplant wait, inotropic support in hospital may be considered. However, prolonged hospitalizations result in exposure to nosocomial organisms, end-organ dysfunction, and increased costs.

Case: the waiting list

A 35-year-old woman was referred to the clinic with a 1-month history of progressive fatigue and abdominal complaints, including nausea, vomiting, and right upper quadrant pain. Her lab work was unremarkable. Her symptoms did not improve with a proton pump inhibitor. An abdominal ultrasound scan revealed a large, congested liver, so an echocardiogram was performed which revealed severe diffuse left ventricular dysfunction. On arrival in clinic, she is pale and diaphoretic with cool

extremities, a pulse of 120 and regular and blood pressure of 80/64 mmHg. She is euvolemic on examination. It is immediately apparent that she requires hospital admission for aggressive evaluation and therapy. Emergent catheterization and heart biopsy reveal a cardiac index of 1.5 L/min per m², pulmonary capillary wedge pressure (PCWP) 20 mmHg, systemic vascular resistance (SVR) 2500 dyn·s/cm⁵, normal coronary arteries, and no evidence of myocarditis. Milrinone therapy is begun with no improvement and a slight decrease in blood pressure. The patient is unable to tolerate even 6.25 mg captopril and develops progressive renal insufficiency and increased liver function tests along with increasing ventricular ectopy. Although heart transplant evaluation has not been completed, no obvious contraindications are apparent. The patient undergoes emergency implantation of a HeartMate left VAD as a bridge to allowing complete evaluation for heart transplantation. Her condition stabilizes with left VAD support and, after clinical rehabilitation, she is evaluated for transplantation and placed on the waiting list.

Infections should be treated aggressively because systemic infection constitutes a contraindication to transplantation. This can be problematic in patients with indwelling devices such as assist devices or catheters utilized for chronic intravenous infusions. In the absence of bacteremia or distant seeding, local device or catheter infections are not necessarily a contraindication to transplantation.

Pretransplant blood product transfusions should be avoided if possible to avoid the possibility of sensitization. Leukocyte depletion may decrease the risk of sensitization, and should be used if blood products must be given to transplant candidates. However, because sensitization can render transplantation difficult or impossible, exposure to blood products should still be minimized. This can be problematic because anemia is common in heart failure patients. Patients should be instructed to report all transfusions to the transplant center to allow follow-up testing for sensitization.

Patients with a panel-reactive antibody (PRA) >10% or those demonstrating reactivity to common antigens should undergo prospective cross-matching before transplantation, although “virtual” cross-matching (avoiding unacceptable donor antigens) may be possible. The time constraints imposed by traditional cross-matching can be problematic, especially with distant or unstable donors or recipients in whom an extended explantation is anticipated. When the degree of sensitization renders transplantation unlikely, desensitization should be considered. This entails antibody removal or binding coupled with suppression of antibody production. Serial PRA screening is performed every 4–8 weeks in patients sensitized at the time of evaluation or on VADs (as sensitization can occur, even without additional antigen exposure), and 2 and 4 weeks after transfusion of any blood products.

Routine pretransplant follow-up with the listing transplant center, usually at 4- to 8-week intervals, is recommended. However, in practice, status 2 patients are often followed up less frequently based on the reduced likelihood of imminent transplantation compared with patients who are status 1A or 1B. Close follow-up permits early intervention for conditions that would complicate or preclude transplantation (e.g. infection, pulmonary hypertension), and also allows modification of care and change in status if heart failure worsens. To accurately monitor pulmo-

nary vascular disease, serial right heart catheterizations with vasodilator challenge (if appropriate) are performed at least every 3–6 months. A pulmonary vascular resistance of ≤ 2.5 Wood units and/or a transpulmonary gradient of ≤ 15 mmHg on optimized medical therapy (including vasodilator infusions) portends a low risk of post-transplant right ventricular failure and mortality. Resistant pulmonary vascular disease, especially with elevated left-sided filling pressures, may respond to left VAD support, but is generally not regarded as an indication for mechanical support in the absence of advanced clinical disease.

The benefit of optimized medical and surgical pretransplant management is incremental over time, so serial prognostic assessments of listed patients should be performed, particularly measurement of functional capacity by cardiopulmonary exercise testing and contractility by echocardiography. Patients who experience clinical improvement can be removed from the waiting list, either temporarily or permanently, if updated prognostic evaluation suggests a declining benefit of transplantation. More importantly, delisting should be considered for patients who no longer meet the criteria for transplantation. This is often a difficult conversation but can be made easier by taking the time to discuss this possibility with patients and their families at the time of listing/evaluation.

Key points 8.3 The close follow-up by the transplant center needed by patients listed for transplantation

Clinical assessment at least every 4–8 weeks

Right heart catheterizations every 3–6 months

Plasma reactive antibody levels every 4–8 weeks if positive at the time of evaluation or for patients on ventricular assist devices and 2 and 4 weeks after transfusion of any blood products

Cardiopulmonary exercise testing and echocardiography every 6–12 months for clinically stable patients

Donor selection and management

General donor criteria

The first step in defining a potential donor is confirmation of brain death. The organ/tissue donation

consent form must then be completed and signed. When the organ procurement team arrives at the donor hospital, the responsible surgeon reviews the chart and confirms the declaration of brain death and consent. It is also crucial to confirm the donor blood type and the UNOS ID. Currently, US centers have instituted at least two separate checks of donor/recipient ABO compatibility, as mandated by UNOS. It is important to confirm ABO type in donors who have had multiple blood transfusions, because massive type O transfusions at resuscitation have resulted in false ABO typing.

Certain factors are a contraindication to donation of any organ, including HIV positivity and major extracranial malignancy. Factors that specifically preclude heart donation include penetrating cardiac trauma, known cardiac disease, or prolonged cardiac arrest with intracardiac injections, although cardiopulmonary resuscitation (CPR) is not an absolute contraindication to organ use.

In 1971, criteria describing the ideal cardiac donor included age <30, no significant medical problems, no history of substance abuse, ischemic time <2h, and no evidence of infection. Over time, significant changes have been made to these criteria based on experience and the realities of the donor shortage. Heart donor selection criteria vary among centers, but expanded donor criteria at some centers include age >60 years, echocardiographic abnormalities, ischemic time up to 7 h, donor/recipient size mismatch up to 70%, positive donor urine/sputum cultures, significant pressor/inotrope requirements, donor substance abuse, and longstanding diabetes mellitus. Judgments need to be carefully made when evaluating marginal donors, and additional evaluation may be required to assure donor suitability. It is important to realize that donor selection is as much a function of the recipient's medical condition as it is that of the donor.

Tests routinely performed to evaluate the suitability of a donor heart include the following:

- Blood tests, including CBC, chemistry, coagulation, blood type, serology.
- 12-lead EKG (non-specific ST changes associated with brain death do not preclude donation)
- Cardiac enzymes, including creatine phosphokinase MB and troponin (positive cardiac enzymes do not preclude use of the heart, but warrant more careful evaluation)

- Chest radiograph
- Echocardiogram (transthoracic or transesophageal, if needed); echocardiography is used to eliminate donors with abnormalities such as valvular pathology or septal defects; if the donor has a regional wall motion abnormality or ventricular hypertrophy, donor suitability needs to be carefully evaluated; if there is mild, diffuse hypocontractility in a young donor with no history of or reason for cardiac dysfunction, heart donation can still be considered
- Coronary angiography: we recommend coronary angiography for male donors >40 years and female donors >45 years, particularly if the donor has a history of hypertension, smoking, diabetes, cocaine use, or focal EKG or echocardiographic abnormalities. If coronary angiography is not available, direct palpation for plaques by an experienced donor surgeon may represent the only, albeit unreliable, method to evaluate the coronary arteries.

Donor suitability

Whether or not to accept older donors needs to be determined case by case, depending on the recipient's age and urgency for transplantation. The predicted ischemic time also plays a role in determining the suitability of a potential donor. Currently, most centers accept an ischemic time up to 4 h. Although reports indicate that longer ischemic times can be tolerated, especially by younger heart donors, this needs to be assessed individually, particularly in donors considered "marginal" for other reasons. It is not completely elucidated to what extent longer ischemic times affect outcomes because a longer ischemic time may result not only in primary graft failure but also in the need for prolonged inotropic support, a prolonged intensive care unit (ICU) stay, and an increase in cardiac allograft vasculopathy.

Frequently, donors are on inotropic and/or vasopressor support. The need for such support should be carefully assessed. It is helpful to have experienced on-site clinicians to evaluate and manage potential donors. Optimizing volume status, acid-base status, serum electrolytes (especially calcium), body temperature, oxygenation, and hematocrit often reduces the need for inotropic or vasoconstrictor medications.

Donor hearts with cardiac damage such as cardiac contusion or that have received open cardiac massage are not suitable for transplantation. However, it is

difficult to diagnose cardiac contusion before opening the chest. Therefore, careful evaluation in the donor operating room is essential. A history of brief closed chest CPR does not preclude the heart from transplantation.

The most common substance abuse is cigarette smoking. If there is a significant history of tobacco use, particularly in an older donor, coronary angiography may be warranted. The second most common substance abuse is alcohol abuse. Caution is suggested as preclinical alcoholic cardiomyopathy could lead to postoperative graft dysfunction.

Illicit drug use includes primarily marijuana and cocaine. Marijuana use by the donor does not preclude heart donation. However, cocaine can cause vasospastic coronary disease and needs particular attention. Various poisons, such as carbon monoxide and cyanide, can cause brain death. The transplant team needs to carefully evaluate such donors, although successful heart transplantations from donors with these exposures have been reported.

It is relatively common to find a positive culture, especially urine or sputum, in donors. However, transmission of bacterial infection from the donor to a heart recipient is rare. When the results of the donor culture and sensitivity tests become available, perioperative antibiotic coverage of the recipient should be modified appropriately. Currently, the use of hepatitis B- and C-positive donors is not recommended, except perhaps for critically ill transplant candidates felt not to have other options.

Donor/Recipient matching

The donor and recipient must be of compatible blood type. If a patient waiting for heart transplantation has a PRA >10%, a prospective cross-match or “virtual” cross-match is mandatory before transplantation. Donor size is matched to recipient size on a weight and height basis. Many centers avoid discrepancies >20%, although successful transplants have resulted with mismatches as great as 50%. Size match crudely estimates that the donor heart is large enough to generate adequate cardiac output to support the recipient, but not so large as to preclude sternal closure or promote tamponade. Many transplant recipients have dilated hearts and, therefore, the pericardial cavity is large enough to accept a larger heart. Although weight and height are the current standards

used to assess donor/recipient size compatibility, donor weight is a poor surrogate of heart size or function, and the transplant team needs to recognize this limitation and evaluate each donor/recipient combination case by case.

To prevent post-transplant right heart failure, some centers purposefully use larger donors for recipients with pulmonary hypertension. Although this strategy is theoretical, there are no data to support the practice. On the other hand, use of a smaller donor for recipients with known high pulmonary vascular resistance can be problematic because the donor right heart is not conditioned to pump against high afterload and may develop severe right heart failure early after transplantation.

Donor management

The management of potential deceased donors is discussed in detail in Chapter 3. Continuous monitoring of the donor, including use of an arterial line, central venous pressure monitoring (CVP), and pulse oximetry is recommended. A pulmonary artery (Swan-Ganz) catheter may be helpful in the management of an unstable donor. Attempts should be made to maintain a systolic arterial pressure of 100 mmHg and a mean arterial pressure of 60–65 mmHg. Brain death involves an initial catecholamine surge, followed by depletion, resulting in hypotension related to vasodilation. Hypotension should be treated by replacing fluids (colloid, crystalloid, or packed red blood cells if the hematocrit falls to <25%); if hypotension persists despite apparent euolemia (CVP = 10–15 mmHg), low-dose inotropic or vasopressor support may be needed. Due to the relative deficiency of vasopressin in brain death, intravenous arginine vasopressin (1–4 units/h) can be effective in maintaining hemodynamic stability in donors. In addition, because of a relative thyroid hormone deficiency in brain death, intravenous levothyroxine (T₄, 20 µg bolus and 40–80 µg/h) may also help reduce inotrope and vasopressor requirements.

Urine output should be maintained at >2 ml/kg per h. Frequently, due to brain death and diabetes insipidus, urine output exceeds 500 mL/h. In such cases, CVP monitoring is essential and desmopressin acetate (a single bolus of 0.5 µg i.v. or infusion at 0.05–0.1 units/min) is given. Fluid replacement should match hourly urine output plus 100 mL, and

electrolytes should be monitored and replaced aggressively.

Serial arterial blood gases define the adequacy of ventilation and acid–base status. When managing a donor for multiorgan recovery, a careful balance considering each solid organ is mandatory. Although hydration maintains cardiac and renal function, it is harmful for the lungs; on the other hand, vasoconstriction compromises abdominal organs. Ultimately, striking a balance between hemodynamic stability and end-organ perfusion, while maintaining adequate fluid balance, is the best approach to allow successful recovery of all possible organs.

Case: donor selection and management

A 20-year-old man is declared brain dead 1 day after admission to the neuro-ICU following a rollover car accident. Upon initial declaration of brain death, he is tachycardic with a blood pressure 82/30 mmHg on dobutamine 5 µg/kg per min, dopamine 20 µg/kg per min, norepinephrine 6 µg/kg per min, and vasopressin 6 units/h with a CVP of 1 cmH₂O. There is no evidence of chest wall trauma, no history of cardiac disease, and the troponin is normal. Echocardiogram reveals mild diffuse left ventricular (LV) dysfunction with an LV ejection fraction (LVEF) of 40%. The heart has been turned down for transplantation by three centers but it is requested that the OPO optimize donor volume status, wean the inotropic and vasopressor support as much as possible, and repeat an echocardiogram in 6 h. Six hours later, with a CVP of 7 cmH₂O, the potential donor's blood pressure is 100/60 mmHg on only dobutamine 5 µg/kg per min and vasopressin 4 units/h and the echocardiogram reveals an LVEF of 55%. The heart is transplanted into a 40-year-old man who has been waiting for a heart for more than a year with recent clinical deterioration. The transplant recipient does well and is discharged from the hospital 8 days post-transplantation.

Surgical techniques/perioperative management/early complications

Preparation of the recipient

Recipient preparation begins long before an organ becomes available. A complete history and physical examination with frequent monitoring and updating are important because many transplantations occur off-hours when personnel are at a minimum. Nevertheless, an updated history and physical exami-

nation should be completed on admission for transplantation, along with routine laboratory evaluation including: complete blood count (CBC) with differential, coagulation profile with platelet count, electrolytes, creatinine, liver function tests, and a type and cross-match. A chest radiograph should be obtained and the patient made nil by mouth. When time is a concern, the patient may be admitted directly to the operating room with labs drawn at the time of line placement and the chest radiograph obtained there.

Upon donor team confirmation of organ suitability, the recipient can be intubated and anesthesia induced, based on estimated donor organ arrival time and estimated recipient surgical time. Central venous access is obtained and a Swan–Ganz catheter floated into the pulmonary artery. Although it is helpful to know the immediate preoperative pulmonary artery pressures, sometimes the large right atrium and right ventricle make it difficult to float the Swan–Ganz catheter. In these patients, the Swan–Ganz catheter may be floated into the right atrium, where the surgeon can find it and place it under direct vision into the pulmonary artery at the time of implantation. Arterial pressure monitoring should begin, and a Foley catheter should be inserted. Some surgeons opt to dissect out the femoral vessels in patients who have undergone previous thoracic operations to allow cannulation should there be a need to go on emergency bypass. Routine femoral dissection should not, however, be performed, because it can be a source of complications including seroma, wound infection, pain, and restriction of mobility.

Timing of recipient explantation is variable. Some centers wait until the donor heart has arrived in the operating room and others time the explantation so that implantation may occur immediately as the donor heart arrives (Figure 8.4). Dissection in the naive chest can take as little as 45 min. However, complex reoperative dissection, including that performed in patients with a VAD *in situ*, may require more than 2 h. After sternotomy, a pericardial well is created by retracting the pericardium laterally and attaching it to the sternal retractor with 2/0 silk stay sutures. Bone wax should be avoided on the sternotomy edges because it could produce an infectious nidus in the postoperative period.

Aortic cannulation is best done high on the lesser curvature of the arch, allowing excision of the proximal aorta if prior bypass graft sites exist. The caeve

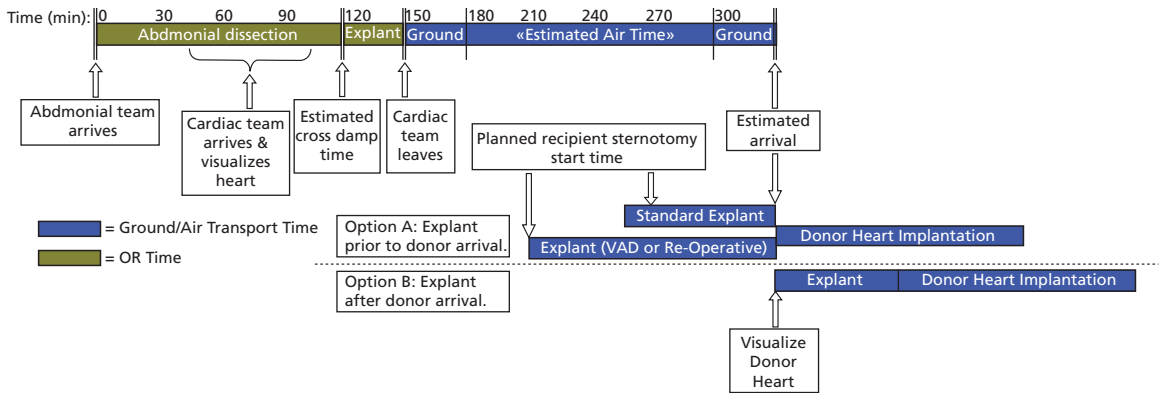


Figure 8.4 Timelines for donor and recipient surgeries for cardiac transplantation. Close coordination and communication between recipient and donor teams is essential.

should be cannulated as far distally as possible and secured with umbilical tape snares around the vessel and cannula. Right-angled metal-tipped cannulae are preferred because they allow smaller purse-string suturing.

The great vessels are dissected free and the aorta is transected just above the sinotubular junction, care being taken while dividing the back wall of the aorta to avoid injuring the right pulmonary trunk. This allows the surgeon to trim the aorta based on donor aortic length and possible excision of prior graft sites. The pulmonary artery is divided just distal to the pulmonary valve. Care must be taken to keep the plane of dissection parallel with the orifice of the pulmonary valve to prevent foreshortening of the pulmonary artery cuff, which leads to a technically difficult anastomosis.

If a biatrial implantation is planned, the left atrial dome is incised just below the aorta and the incision is carried around in a counterclockwise fashion into the atrial septum. Next, the right atrium is incised at the base of the appendage and this incision extended through the septum to the base of the coronary sinus. The remainder of the left atrial cuff is then excised from the atrial dome to the coronary sinus in a clockwise direction (Figure 8.5a). If bicaval implantation is planned, the left atrial resection proceeds as described above. However, the right atrium is divided at the cavoatrial junctions, leaving a short cuff of atrium for later anastomosis (Figure 8.5b). A longer cuff is preferable on the inferior vena cava (IVC),

because it tends to retract toward the diaphragm after transection. Finally, the left atrium should be inspected for thrombus and hemostasis of the posterior pericardial space should be achieved before implantation because this region is difficult to visualize after implantation.

Explantation techniques

Donor

Donor heart explantation is performed via a median sternotomy. Communication between the abdominal and thoracic teams is essential for successful procurement on both sides. Upon sternotomy, the donor heart is examined for contusion, infarction, congenital anomalies, aneurysmal disease, or vascular anomalies. The coronary arteries are palpated for plaques and global function is assessed. Once suitability is confirmed, communication to the recipient team as to the expected cross-clamp time must occur (see Figure 8.4).

We recommend that the donor team call the recipient team on arrival at the donor hospital to confirm that there are no delays in the organ procurement. The second call is usually after visualization to confirm the condition of the organ; a third call should be made upon leaving the donor operating room to confirm arrival time at the recipient center.

After the abdominal team has completed dissection, 300 U/kg of heparin is administered and the aorta is cannulated for delivery of cold preservation solution. It is our preference to use 1000–2000 mL of the UW

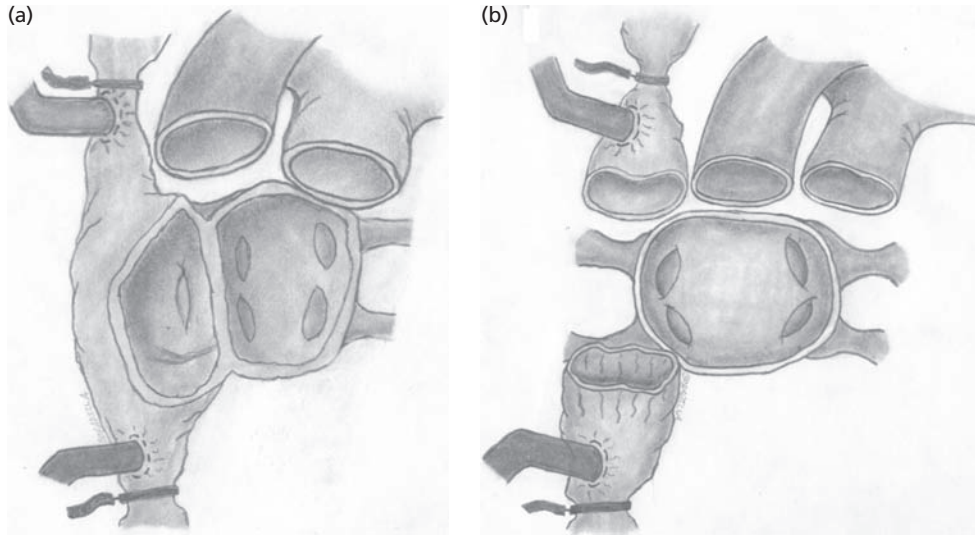


Figure 8.5 Recipient preparation for cardiac transplantation using the standard biatrial (a) and bicaval (b) techniques.

solution. When the anesthesia, abdominal, and thoracic teams are prepared, the heart is decompressed by incising the IVC and left inferior pulmonary vein, the aorta is cross-clamped and the cold preservation solution is infused via the aortic root cannula. Vigorous suction is applied to keep the pericardial well clear and rapid transection of the IVC, pulmonary veins, aorta, superior vena cava (SVC), and pulmonary artery at its bifurcation occurs.

Back-table procedures

Upon return to the recipient institution, back-table dissection prepares the donor heart for implantation. The heart is again inspected for defects – specifically, the foramen ovale is probed for patency. If a patent foramen ovale is found, it is closed in two layers using 4/0 monofilament non-absorbable suture. Next, the pulmonary vein fossae are connected to form a single left atrial cuff for anastomosis. If a biatrial procedure is planned, the SVC is ligated using silk ties and oversewn with a 3/0 or 4/0 monofilament, and the right atrium is incised from the lateral-most portion of the IVC to the base of the right atrial appendage, avoiding the sinus node. If the left atrial appendage was incised to vent the heart during pulmoplegia for simultaneous lung procurement, this should be repaired at this time.

Implantation techniques

Heterotopic transplantation

Heterotopic transplantation is mostly of historical interest. This technique leaves the native heart in place and implants the donor heart in the right chest. This technique was utilized in cases of significant donor-recipient size mismatch or irreversibly elevated pulmonary vascular resistance.

Total excision of recipient atria

Total excision of recipient atria (TERA) and pulmonary vein implantation were first described in 1991. This technique required total excision of the donor atria along with extra lengths of the cavae. With TERA, the donor superior and inferior pulmonary veins are resected on the back table to form a single orifice for the right and left veins. Implantation then proceeds with the left then right pulmonary vein islands, the IVC and SVC, and finally the aorta and pulmonary artery. The added anastomotic time and technical difficulty have prevented widespread acceptance of this technique.

Standard (classic-biatrial) technique

Implantation starts at the base of the left atrial appendage and extends clockwise toward the atrial

septum, using a double-armed 3/0 monofilament. Once the septum is reached inferiorly, the second arm is used to complete the superior portion of the left atrial anastomosis. The right atrial anastomosis is completed starting at the mid-portion of the donor right atrium, again with a double-armed 3/0 monofilament. This anastomosis proceeds inferiorly, then superiorly, incorporating the previous septal suture line. Finally, the pulmonary artery and aorta are anastomosed end to end using a running 4/0 monofilament suture.

This biatrial procedure results in a “snowman” or hourglass-shaped atrium. This disruption of atrial geometry may lead to tricuspid and mitral valvular dysfunction and sinus node dysfunction.

Bicaaval technique

Concerns over valvular dysfunction and atrial dysfunction resulted in the development of an implantation technique to better preserve atrial anatomy. Sievers and colleagues were among the first to describe the bicaaval implantation technique in 1991. Recipient cardiectomy proceeds as previously described, and implantation begins with the left atrial cuff as in the standard technique. Care should be taken to evert the cut edges of the atrial wall to avoid exposed free wall inside the atrial chamber – a potential source of postoperative thrombus. After the left atrial anastomosis is completed, some centers vent the left atria via the appendage and run ice-cold saline to de-air the heart and prevent premature re-warming. It is our practice to wrap the heart in a cold, saline-soaked laparotomy pad and use continuous carbon dioxide flow over the pericardial well to aid in de-airing. At this point, a Swan–Ganz catheter may be manually placed under direct visualization through the SVC and into the pulmonary artery. Attention is then turned to the caval anastomoses, performed end to end using 4/0 monofilament suture; care must be taken not to purse-string the anastomoses. The pulmonary artery is then trimmed and an end-to-end anastomosis performed with 4/0 monofilament; care must be taken here to avoid rotation of the anastomosis. Finally, the aortic anastomosis is performed using 4/0 monofilament as well; however, as the medial wall of the aorta is often stripped of adventitia from the separation from the pulmonary artery, we routinely use reinforcing bovine or autologous pericardial strips.

Since its introduction, the bicaaval technique has become the procedure of choice, because of its ability to preserve right atrial conformation, and thus minimize tricuspid regurgitation and nodal arrhythmias. A survey by Aziz et al. in 1999 showed that, among 210 transplant centers worldwide, the bicaaval technique was preferred. Multiple groups have documented various benefits to the bicaaval technique including:

- improved cardiac output/index, ejection fraction, and exercise tolerance
- lower pulmonary artery pressures and atrial volumes and improved right ventricular function
- lower incidence of atrial arrhythmias/blocks
- reduced mitral and tricuspid regurgitation.

Perioperative management

Once all anastomoses are completed, the patient is placed in the Trendelenburg position, the aortic cross-clamp removed, and the heart de-aired via an aortic root vent. Transesophageal echo (TEE) is instrumental in confirming the removal of all air from the cardiac chambers, as well as for assessing graft function. After de-airing and return of sinus rhythm, the patient is weaned from cardiopulmonary bypass. We utilize inotropic support in all patients, either dobutamine or milrinone, because cardiac function tends to transiently decline 6–8 h post-transplant. After successful weaning of cardiopulmonary bypass, temporary pacing wires are placed in the right atrium and right ventricle, and mediastinal/pericardial drains are placed.

The immediate postoperative period provides many challenges. Vasodilatory hypotension, bleeding, early allograft dysfunction, sinus node dysfunction, right heart failure, and acute renal failure are only a few of the obstacles in the early postoperative period. Continuous invasive hemodynamic monitoring of arterial and pulmonary arterial pressure and back-up pacing are essential. Slow weaning of vasopressor and inotropic support should be attempted over the first 24–48 h. Typically, our institution weans vasoconstrictors first and maintains inotropic support for at least 24 h. It also monitors mixed venous oxygen content. Mixed venous O₂ monitoring allows a physiologic measure of adequacy of systemic perfusion. Attempts should be made to extubate early after return from the operating room.

Early complications

Hypotension

Hypotension can be multifactorial, but tamponade must always be considered. The use of aprotinin and meticulous attention to hemostasis during implantation are of utmost importance. Special attention should be paid to the medial wall of the aorta and the cut edges of the recipient atrial cuffs, as these tend to be foci of bleeding. Given that the mediastinal drains are not obstructed and output is minimal, other causes of hypotension should be considered. Often, systemic inflammatory response syndrome-like conditions evolve as a result of cytokine activation from cardiopulmonary bypass use. Treatment with vasoactive catecholamines, such as norepinephrine, should be initiated if this is suspected. We advocate the use of arginine vasopressin, because it may serve to replace depleted stores, especially in the decompensated heart failure patient.

Early allograft dysfunction

Early allograft dysfunction may also cause postoperative hypotension, characterized by poor cardiac output/index and reduced mixed venous oxygenation. This phenomenon may account for a third of transplant-related deaths, and may be due to ischemia–reperfusion injury, prolonged ischemic times (>4h), unanticipated donor heart dysfunction, and/or hyperacute rejection. Recent evidence has implicated an inhibitory G-protein-associated pathway, which impairs cardiac contractility and is unregulated in ischemia–reperfusion conditions. Inotropic support is, however, usually enough to maintain patients through the period of ischemia–reperfusion injury-related graft dysfunction, which peaks at 6–8h posttransplantation. If inotropic support is inadequate to maintain end-organ perfusion, mechanical circulatory assistance (left VAD, right VAD, bi-VAD) should be initiated early.

Hyperacute rejection, which may present as a “stone heart,” is a more daunting complication, seen more commonly in people with elevated PRAs. Donor-recipient cross-matching has helped reduce hyperacute rejection in the current era.

Arrhythmias

Bradycardia is the most common postoperative rhythm disturbance. As the resting rate of the dener-

vated heart varies from 90–115 beats/min, rates less than this are often due to sinus node injury or ischemia. Other implications of the denervated heart are discussed later in this chapter. We recommend back-up use of a pacemaker targeted to 90–110 beats/min, especially in the immediate postoperative period. Atrial fibrillation or flutter is uncommon, and may be a sign of graft rejection.

Right heart failure

Right heart failure (RHF) may develop due to right-sided susceptibility to poor myocardial preservation, recipient pulmonary hypertension, and/or ischemia–reperfusion injury. RHF is suspected in the setting of an elevated CVP and/or poor cardiac index. If the patient is intubated, TEE allows optimal visualization of the right heart, compared with standard transthoracic echo. Inotropic support with milrinone is preferred because it also dilates the pulmonary vascular bed. If pulmonary hypertension is present, inhaled nitric oxide may be added to decrease right ventricular afterload. Tight control of volume status guided by pulmonary artery catheter data is essential, and excess fluid should be eliminated with diuretics or continuous venovenous hemofiltration (CVVH).

Renal failure

Acute renal dysfunction may be related to ischemia from cardiopulmonary bypass, thromboemboli, perioperative hypotension, nephrotoxic medications, or intrinsic renal disease. Unfortunately, many cardiac transplant recipients also have dysregulation of normal natriuretic responses, and do not respond appropriately to volume overload. Aggressive volume control with diuresis is needed to prevent right heart strain, especially in the early postischemic phase. In patients whose urine output cannot be matched to the fluid infusion associated with administration of vasopressors, inotropes, and blood products, renal replacement therapy must be entertained. CVVH allows for removal of large volumes of fluid and may serve as a bridge until renal function returns.

Physiology of the denervated heart

During donor heart implantation, the nerve supply is not anastomosed, and therefore the transplanted heart is denervated, at least early after

transplantation. This denervation results in an increased resting heart rate (due to lack of vagal tone) and an altered physiologic response to exercise. The increase in cardiac output produced by the transplanted heart early in exercise depends on an increase in venous return due to peripheral muscle pumping of blood back to the heart and the Frank–Starling mechanism. The increase in heart rate with exercise is delayed and prolonged, as it is related to an increase in circulating catecholamines rather than a withdrawal and later increase in vagal tone. With time after transplantation there is partial sympathetic reinnervation, as shown by an increase in coronary sinus norepinephrine in response to intravenous tyramine (which causes degranulation of neural vesicles containing norepinephrine) or sustained handgrip, MIBG (¹³¹I-labeled *meta*-iodobenzylguanidine) cardiac uptake on nuclear scanning, PET (positron emission tomography), and an improved heart rate response to exercise. Although partial vagal reinnervation has been suggested, this has not been confirmed to be of clinical relevance.

Early after cardiac transplantation, due to the denervated state, symptoms of myocardial ischemia may be absent or atypical. However, later after transplantation angina may occur. Another clinically relevant implication of the denervated state is that digoxin is relatively ineffective for treating supraventricular tachycardia because the drug usually works in this regard by inhibiting vagal tone. Similarly, atropine is ineffective for treating bradycardia. Supraventricular tachycardia should be treated with direct-acting drugs, including procainamide (which is relatively safe if LV function is normal, and, as vagal tone is not withdrawn, an increase in ventricular response does not occur) or amiodarone. As the denervated heart is exquisitely sensitive to adenosine, adenosine should be used cautiously and in low doses, if at all. Isoproterenol or other direct β stimulants should be used for acute treatment of bradycardia.

Immunosuppression after heart transplantation

Immunosuppressive management after heart transplantation epitomizes the art of medicine. The transplant physician starts with an immunosuppressive

protocol that is largely driven by the endomyocardial biopsy grade, and then individualizes therapy based on time since transplantation, risk of rejection, prior rejection history, the presence of hemodynamic compromise, and the presence of cardiac allograft vasculopathy. Standard immunosuppression consists of a combination of drugs in doses that lessen individual toxic effects but together inhibit the immune response. Most centers use triple-drug therapy with corticosteroids, a calcineurin inhibitor CNI (tacrolimus or cyclosporine), and an antiproliferative drug (mycophenolate mofetil or azathioprine), but there are almost as many immunosuppressive protocols as there are heart transplant centers.

Early rejection prophylaxis

Early rejection prophylaxis refers to immunosuppressive therapy given perioperatively and in the first 2 weeks after transplantation. The primary goal is to prevent or delay allograft rejection until ischemia-induced graft dysfunction resolves. Patients are given high doses of intravenous methylprednisolone perioperatively, combined with a CNI and mycophenolate mofetil (MMF) or azathioprine. CNI dosing is determined by whole blood levels and adjusted for creatinine because of the nephrotoxicity associated with these drugs. Initial cyclosporine doses are in the 5–10 mg/kg per day range. Target CSA levels are in the 175–350 ng/mL range, with the highest target levels immediately after transplantation. Less is known about optimal tacrolimus dosing for heart transplant recipients. Initial doses range from 0.075 mg/kg per day to 0.15 mg/kg per day with therapeutic levels of 10–20 ng/mL. MMF is dosed 1000–1500 mg twice daily and azathioprine 2 mg/kg daily. Dosing of all immunosuppressive drugs must be modified if side effects occur.

Heart transplant recipients develop some degree of allograft tolerance, regardless of the early immunosuppression protocol; however, whether tolerance is enhanced by specific protocols remains uncertain. Studies comparing triple-drug immunosuppressive prophylaxis with and without anti-lymphocyte therapy have shown that OKT3 delayed the time to first rejection, but did not confer additional immunologic benefit over triple-drug immunosuppression. A recent report from the Cardiac Transplant Research

Database (CTRD) revealed that anti-lymphocyte therapy was most beneficial in patients at high risk for rejection-mediated death (long-term VAD support, black ethnicity, and extensive HLA mismatching). However, perioperative OKT3 may increase the risk of infection, especially cytomegalovirus (CMV), and lymphoproliferative disease, especially when a cumulative dose of OKT3 exceeds 75 mg.

Antibodies to the interleukin-2 receptor (IL-2R – daclizumab and basiliximab) have also been used as perioperative immunosuppressive prophylaxis in heart transplantation. In a randomized study, perioperative daclizumab with triple maintenance immunosuppression decreased early rejection. However, there was an increased risk of infectious death in patients who received daclizumab and also received anti-lymphocyte therapy (for renal sparing or to treat rejection). Therefore, combined use of IL-2R antibodies and anti-lymphocyte therapy is not recommended.

Triple-drug immunosuppression without perioperative antibody induction therapy yields excellent patient survival. Although data demonstrate the effectiveness of anti-lymphocyte antibodies in treating recalcitrant rejection, the value of these agents for routine perioperative use remains unclear. Anti-lymphocyte therapy provides no clear benefit compared with standard triple-drug immunosuppression and has been associated with an increased risk of infection and lymphoproliferative disorders. As these agents can produce a severe systemic inflammatory response, and as foreign proteins can induce an immune response limiting subsequent effectiveness, many centers reserve use of anti-lymphocyte agents for refractory rejection. However, perioperative anti-lymphocyte antibody therapy may be valuable to allow delayed initiation of CNIs in patients with renal insufficiency and for maximization of immunosuppression for patients at greater risk for rejection.

Maintenance immunosuppressive strategies

Steroid withdrawal Concerns about the harmful effects of chronic steroid use have stimulated interest in immunosuppressive regimens that eliminate steroids without endangering graft survival. In a review of 670 heart transplant patients from 26 centers in the USA, survival of patients on steroid-free regimens was comparable to that on maintenance steroids.

Indeed, data suggest that the ability to wean patients from steroids identifies a group with a lower propensity to reject and a better long-term prognosis.

Yacoub et al. (see Further reading) introduced the concept of steroid-free immunosuppression in 1985, reporting a 1-year actuarial survival rate of 82% in 67 patients in whom steroids were stopped at 3 days while receiving perioperative anti-thymocyte globulin, and maintenance therapy with cyclosporine and azathioprine. There is currently no consensus on the optimal time to withdraw steroids, but two approaches have evolved: early withdrawal (within 1 month), usually with perioperative anti-lymphocyte therapy, or late withdrawal (>3 months post-transplantation) with or without perioperative anti-lymphocyte therapy. A prospective, randomized trial compared double (steroid free) with triple therapy in 112 patients, and reported similar 5-year survival and systolic function if recurrent rejectors in the double-therapy group were converted to maintenance steroids. The Utah program has the largest experience with early steroid withdrawal, both with and without perioperative OKT3, reporting 50–60% 1-year and 40–50% 2-year freedom from maintenance steroids. As most acute rejection occurs in the first 6 months after transplantation, many centers delay steroid withdrawal. Steroid weaning after 6 months yields success rates of 69–80%.

There is no optimum steroid withdrawal protocol or criteria for protocol entry or protocol failure. Some centers consider steroid withdrawal in patients at high risk for complications from steroids whereas others select patients at low rejection risk. Some centers consider protocol failure as one rejection episode with hemodynamic compromise, whereas others do not reinstitute maintenance steroids until up to four rejection episodes have occurred. Predictors of successful steroid withdrawal include withdrawal timing, HLA-DR match, male gender, fewer rejection episodes before steroid withdrawal, the degree of allosensitization, and older age. Late steroid withdrawal in patients with a low propensity for rejection predicts the highest success rate.

Benefits of steroid withdrawal include an improved lipid profile, easier to control hypertension, fewer gastrointestinal complications, and an increased growth velocity in children. About half of patients can be withdrawn from corticosteroids without

jeopardizing patient or graft survival, given a few caveats. Perioperative anti-lymphocyte therapy should be considered if steroids are withdrawn early. One rejection episode after steroid withdrawal does not warrant return to steroid use; however, recurrent rejectors should resume steroids. Available data suggest that the greatest success in steroid withdrawal occurs with late withdrawal in patients at low risk of rejection. The low success rate of steroid withdrawal in women especially favors the late approach. Patients intolerant of MMF or azathioprine, or with progressive renal insufficiency indicating the need for lower CNI levels, are not good steroid-withdrawal candidates. Late rejection can occur and warrants surveillance endomyocardial biopsies during weaning and after steroid withdrawal. Close monitoring and optimization of CNI levels is also important.

Calcineurin inhibitors The Collaborative Transplant Study of over 12 000 patients showed superior survival with cyclosporine-based regimens compared with therapy with prednisone and azathioprine alone. In 1994, a microemulsion formulation of cyclosporine was introduced which stabilized the absorption and blood concentration of cyclosporine without increasing toxicity.

The ability of tacrolimus to reverse acute rejection led to investigation of its use as a maintenance immunosuppressive. A small early study comparing tacrolimus with cyclosporine (in combination with both azathioprine and steroids) showed no differences in early rejection or survival, suggesting that tacrolimus was at least as effective as cyclosporine. A more recent and larger study compared a tacrolimus–MMF–steroid regimen with a regimen of cyclosporine–MMF–steroids. The 12-month report from this study revealed no difference in survival between the two groups and a decrease in treated rejection (although only a trend to a decrease in hemodynamically compromising rejection) in the tacrolimus group. Longer-term follow-up data from this study are eagerly awaited. When compared with cyclosporine, tacrolimus has similar nephrotoxic and neurotoxic effects but produces less hypertension, hyperlipidemia, and gingival hyperplasia. There is a propensity for greater glucose intolerance with tacrolimus. CNIs are monitored by whole blood trough levels to guide dose adjustments, although recent data suggest that

cyclosporine concentrations at 2 h after administration may better reflect drug exposure.

Antiproliferative drugs Azathioprine dosages must be decreased if leukopenia (white blood cell count or WBC $<3500/\text{mm}^3$), anemia, or thrombocytopenia occurs. Concomitant use of trimethoprim–sulfamethoxazole or allopurinol increases the risk of leukopenia. MMF has largely replaced azathioprine because of its superior efficacy in reducing rejection, mortality, and possibly cardiac allograft vasculopathy.

TOR inhibitors

Sirolimus and everolimus are members of a new class of immunosuppressants acting through inhibition of a molecular complex, the target of rapamycin (TOR), which inhibits cell proliferation. Everolimus significantly reduces the incidence of rejection and severity of cardiac allograft vasculopathy in patients at 1 and 2 years compared with azathioprine. A similar 2-year benefit was seen with sirolimus.

Treatment of rejection

Acute cellular rejection

Cellular rejection is treated with a short course of intensified immunosuppression, usually steroids. Rejection occurring up to 6 months post-transplantation is treated more aggressively, as is rejection accompanied by hemodynamic compromise or graft dysfunction. Aggressive immunosuppression may involve high doses of intravenous steroids, an anti-lymphocytic agent for 10–14 days, or an increase in CNI target level.

Refractory allograft rejection

Anti-rejection therapy may successfully reverse acute rejection, but the effects may not be sustained. Anti-lymphocyte antibodies, as discussed above, have shown been to reverse refractory rejection. Low-dose methotrexate is also effective in reversing and chronically suppressing recalcitrant rejection in heart transplant recipients. More recently, conversion to tacrolimus has been shown to reverse rejection refractory to continued therapy with cyclosporine. The addition of sirolimus to the baseline immunosuppressive regimen may also be effective. Total lymphoid

radiation, plasmapheresis, and photopheresis have also been used to treat refractory rejection.

Diagnosis of rejection

Rejection surveillance

Rejection remains a lifelong threat to survival, so early recognition and treatment of rejection are a major focus of post-transplant follow-up. There is currently no reliable non-invasive method to diagnose rejection. EKG, echocardiography, radionuclide imaging, and MRI all lack sufficient sensitivity and specificity to replace endomyocardial biopsy, as do cytologic, serologic, and chemical tests. Therefore, patients undergo serial biopsies to detect rejection before loss of graft function. Endomyocardial biopsy is an invasive, yet simple, outpatient procedure with few complications when performed by experienced physicians.

The incidence of rejection is highest in the first 6 months after transplantation, and then falls dramatically (see “Acute rejection”). Therefore, biopsies are performed frequently in the first year. The incidence of rejection is low after 1 year; however, rejection does occur, so most centers continue routine surveillance with endomyocardial biopsy. A typical biopsy schedule would include biopsies weekly for 1 month, every other week for 2 months, monthly for 3 months, and then every 6–8 weeks for the remainder of the first year. During the second year biopsies are performed every 3 months, with biopsies performed every 6–12 months in subsequent years.

Histologic grading system for acute rejection

Acute cellular rejection

Acute cellular rejection manifests histologically as lymphocytic infiltration, with or without myocyte necrosis. It may be accompanied by hemodynamic compromise and can lead to temporary or permanent graft dysfunction. Macrophages and eosinophils may be present, but neutrophilic infiltration suggests a diagnosis other than rejection. Cellular rejection is classified histologically using a standardized grading system as shown in Table 8.4.

Before 1990, there were numerous grading systems for the pathologic diagnosis of rejection in cardiac biopsies. In 1990 the ISHLT developed a standard-

ized grading system for cardiac rejection. This system was widely adopted, but was revised in 2004 to address issues that arose in the previous 15 years. A major issue in the former system concerned grade 2 rejection. As the interobserver variability in diagnosing grade 2 rejection was high and the risk of progression from grade 2 to more severe rejection low, the 1990 ISHLT grades 1A, 1B, and 2 are now combined into the 2004 ISHLT grade 1R.

Antibody-mediated rejection

Antibody-mediated rejection (AMR) is a recognized but controversial entity, associated with poor graft survival. AMR is suspected in the setting of acute graft dysfunction (ventricular systolic dysfunction with or without hemodynamic compromise) in the absence of cellular infiltrate or ischemia. Predisposing factors include prior allosensitization and VAD use. Pathologic findings include immunoglobulin and complement deposition in the coronary vasculature combined with endothelial cell swelling, with or without vasculitis. There is no consensus regarding the histologic or immunologic diagnosis of AMR; however, the revised ISHLT grading scale recommends optional immunofluorescent and immunohistochemical biopsy staining techniques (Table 8.4). If AMR is suspected on light microscopy, further immunohistochemical testing should be performed, along with a serum sample for donor-specific antibody.

Biopsy findings other than rejection

Ischemic injury, the Quilty effect, infection, and lymphoproliferative disorder all cause histologic changes that must be distinguished from rejection. Ischemic injury is classified as either perioperative or related to cardiac allograft vasculopathy. Perioperative or early ischemia refers to injury sustained during organ procurement and implantation, and is intensified by bleeding, hypotension, and inotropic agents. Commonly seen up to 6 weeks post-transplantation, early ischemia is characterized by contraction band, myocyte or fat necrosis, and myocyte vacuolization. Late ischemia refers to injury from cardiac allograft vasculopathy. As large vessels are not routinely seen on biopsy, the pathologist looks for vacuolization and microinfarcts, secondary changes from ischemic injury.

Table 8.4 ISHLT standardized cardiac biopsy grading: acute cellular rejection and antibody-mediated rejection

Grade 0 R ^a 2005	No rejection	Grade 0 1990	No rejection
Grade 1 R, mild	Interstitial and/or perivascular infiltrate with up to one focus of myocyte damage	Grade 1, mild A – focal B – diffuse	Focal perivascular and/or interstitial infiltrate without myocyte damage Diffuse infiltrate without myocyte damage
Grade 2 R, moderate	Two or more foci of infiltrate with associated myocyte damage	Grade 2, moderate (focal)	One focus of infiltrate with myocyte damage
Grade 3 R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage, ± vasculitis	Grade 3, moderate A – focal B – diffuse	Multifocal infiltrate with myocyte damage Diffuse infiltrate with myocyte damage
Grade 4 R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage, ± vasculitis	Grade 4, severe	Diffuse polymorphous infiltrate with extensive myocyte damage ± edema, ± hemorrhage, ± vasculitis
AMR 0	Negative for acute AMR No histologic or immunologic features of AMR		
AMR 1	Positive for AMR Histologic features of AMR Positive immunofluorescence or immunoperoxidase staining for AMR (positive CD68, C4d)		Humoral rejection (positive immunofluorescence, vasculitis or severe edema in absence of cellular infiltrate) recorded as additional required information

^aR denotes revised grade to avoid confusion with 1990 scheme.
AMR, antibody-mediated rejection.

The Quilty effect refers to nodular endocardial infiltrates seen in up to 20% of biopsies. Quilty lesions are usually confined to the endocardium, but, when lesions invade the myocardium, accompanying myocyte damage makes differentiation from rejection problematic. There is no known relationship between the Quilty effect and rejection, so Quilty lesions require no treatment.

With the exception of CMV and toxoplasmosis, which may be associated with lymphocytic infiltration, infection and PTLD are not commonly seen in biopsy specimens, making confusion with acute rejection less likely.

Case: acute rejection

A 52-year-old woman, gravida 4, para 4, underwent heart transplantation in 2005 due to ischemic cardiomyopathy. Her PRA pretransplant was 0% and her initial post-transplant course was uncomplicated. She was com-

pliant with her medical regimen and follow-up. However, at 8 months post-transplantation, she presented with a several day history of increasing fatigue, dyspnea on exertion, and an increase in her resting heart rate. Echocardiogram showed a decrease in her LVEF to 35%. Coronary angiography revealed no coronary artery disease and biopsy was grade 1R, AMR O. Due to the acute nature of the patient's decline and a strong suspicion for immune-mediated allograft dysfunction, the patient received methylprednisolone 250 mg i.v. daily for 3 days and completed a 2-week course (total of six treatments) of plasmapheresis with intravenous gammaglobulin after the third and sixth plasmaphereses. Fortunately 1 month after presentation, her ejection fraction had improved to 55% and she felt well. Of interest, a PRA drawn at the time she presented with LV dysfunction was 80% and donor-specific antibody was present. Although the patient's improvement is encouraging, she is at high risk for poor long-term outcome because of her presentation with hemodynamic compromise in the absence of cellular rejection.

Functional assessment of the cardiac allograft

Echocardiography is indispensable in the evaluation of the cardiac allograft. The rejecting cardiac allograft typically exhibits diastolic stiffness with preserved systolic function. Echocardiographic features of restrictive physiology include decreases in isovolumic relaxation time, mitral valve pressure half-time, deceleration time, and fractional shortening. Systolic dysfunction is a late finding with rejection.

The hemodynamic findings of acute rejection are also those of a restrictive cardiomyopathy, including pulmonary hypertension and increased end-diastolic pressure. Early diastolic filling tends to be slow rather than fast, so the dip-and-plateau ventricular waveform is not usually seen. Although echocardiographic and hemodynamic evaluation of the cardiac allograft should be routinely performed, neither by itself can accurately diagnose acute rejection.

Outcomes/post-transplant follow-up

Acute rejection

The frequency of rejection is highest early after transplantation; however, the risk for rejection continues throughout the life of the transplant recipient. As shown in Figure 8.6, from the Cardiac Transplant Research Database (CTRD), 62% of adult recipients have a rejection episode (defined as a clinical event requiring augmentation of immunosuppression, and

usually accompanied by an abnormal biopsy) during the first year. Risk factors for recurrent rejection in the first year include a female recipient, a younger recipient, positive recipient CMV serology pretransplant, a female donor organ, OKT3 induction therapy, fewer months since transplantation, fewer months since the last rejection episode, and a greater number of previous infections. Risk factors for rejection >1 year after transplantation are similar, and include female transplant recipient, black recipient race, OKT3 induction therapy, a greater number of rejections during the first year, and prior CMV infection. Fortunately, despite the frequency of acute rejection, there is 97% freedom from death or re-transplantation due to acute rejection at 1 year.

Additional comments should be made concerning a rejection episode with hemodynamic compromise (defined as a decrease in cardiac index, a decreased ejection fraction, clinical signs of low cardiac output, or the need to use inotropic agents). In the CTRD, only 8% of recipients had a rejection episode with hemodynamic compromise in the first 3 years. Risk factors for rejection with hemodynamic compromise early after transplantation included a female or a diabetic recipient. Later after transplantation, black recipient race, older donor age, black donor race, and a diabetic donor were risk factors for the first rejection episode with hemodynamic compromise. Of importance, if rejection with hemodynamic compromise occurred in the presence of cellular rejection of

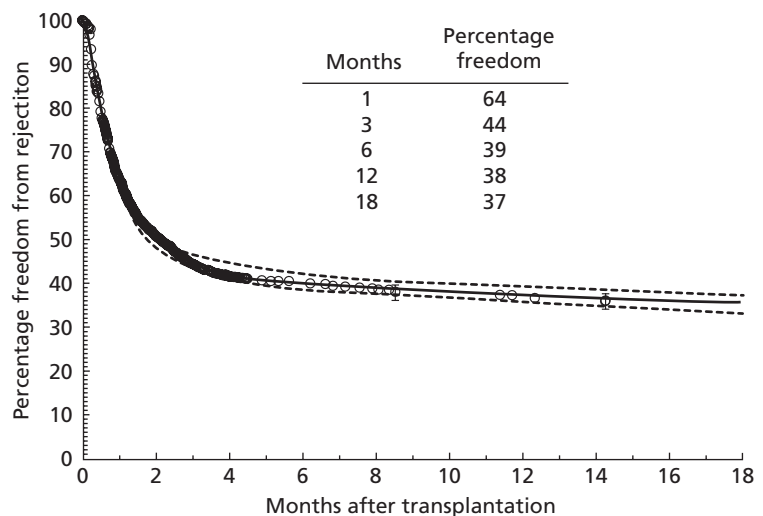


Figure 8.6 Freedom from rejection over time in cardiac transplant recipients: Jan 1990 to June 1991 – $n = 911$; patients with rejection episodes = 495. (Reprinted with permission from Kobashigawa JA, Kirklin JK, Naftel DC, et al. Pretransplantation risk factors for acute rejection after heart transplantation: a multiinstitutional study. The Transplant Cardiologists Research Database Group. *J Heart Lung Transplant* 1993;12:355–66.)

grade 3A or higher, outcome was better than if hemodynamic compromise occurred without cellular rejection on biopsy. It is assumed that many rejection episodes with hemodynamic compromise represent non-cellular-mediated rejection or AMR; however, this is still poorly understood. The exact definition of AMR and appropriate therapy for it still require significant clinical investigation.

Cardiac allograft vasculopathy

Cardiac allograft vasculopathy is a major cause of morbidity and mortality in heart transplant recipients more than 1 year after transplantation. Cardiac allograft vasculopathy is defined as allograft vascular injury induced by a variety of stimuli which leads to a progressive, diffuse vascular obliteration of intramural and epicardial arteries and veins, and the donor segment of the aorta. The diagnosis of cardiac allograft vasculopathy is difficult because the patient frequently has absent or atypical symptoms (due to cardiac denervation) and non-invasive testing is unsatisfactory. The most common test for cardiac allograft vasculopathy is coronary angiography, which is performed annually by most centers, especially early after transplantation. Figure 8.7 shows the

angiographic development of allograft vasculopathy and some of its differences from native coronary artery disease. The left panel shows a coronary angiogram 2 years after transplantation with only minor luminal irregularities. The angiogram in the right panel was performed 3 years after transplantation, when the patient remained asymptomatic. There is significant pruning/disappearance of distal vessels, irregularities in the proximal vessels, and total disappearance of a marginal circumflex branch. As shown, cardiac allograft vasculopathy is more likely to be distal and diffuse compared with the proximal and more focal nature of native coronary artery disease.

Although the most frequent method of diagnosis of cardiac allograft vasculopathy is angiography, the angiogram is insensitive to early disease, and intracoronary ultrasound studies have shown significant intimal thickening before any angiographic abnormalities. Therefore, in studies defining methods to decrease the onset and progression of cardiac allograft vasculopathy, intracoronary ultrasonography is frequently used to quantify maximal intimal thickness and the intimal index (ratio of plaque area to vessel area) (Figure 8.8).

Cardiac allograft vasculopathy begins as smooth muscle cell proliferation followed by concentric

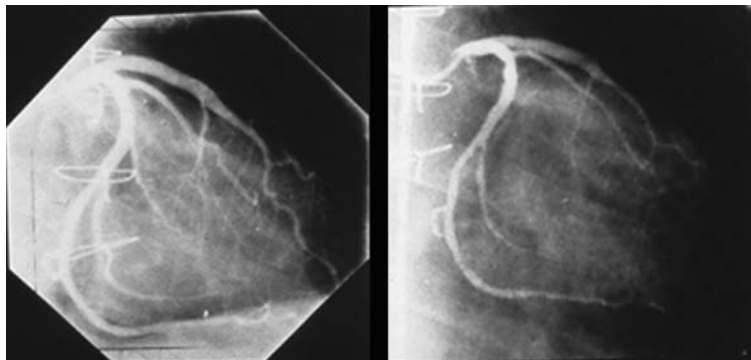
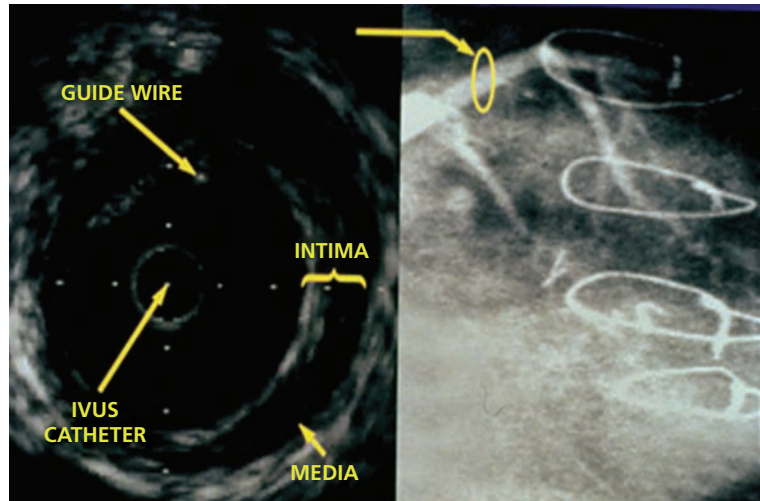


Figure 8.7 Serial coronary angiograms of a cardiac transplant recipient showing the development of cardiac allograft vasculopathy. Panel A shows a left coronary angiogram (right anterior oblique projection) 2 years after transplantation which reveals only minor luminal irregularities. Panel B is an angiogram of the same vessel 3 years after transplantation and reveals severe diffuse disease with pruning of the distal vessels. The patient was

asymptomatic at the time of the 3-year angiogram but died suddenly 2 months later before a suitable donor heart for re-transplantation became available. (Reprinted with permission from Johnson MR. Principles and practice of coronary angiography. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, Braunwald E (eds), *Marcus' Cardiac Imaging*. Philadelphia, PA: WB Saunders Co., 1996: 220–51.)

Figure 8.8 An intravascular ultrasound image (left panel) and coronary angiogram (right panel) of the left anterior descending artery in a cardiac transplant recipient. Although the angiogram appears normal, ultrasonography at the site noted shows significant intimal thickening.



intimal proliferation, with an intact internal elastic lamina. Endothelial expression of MHC (major histocompatibility complex) class II antigens is frequently present. Unlike native coronary disease where cholesterol deposition is extracellular, in allograft vasculopathy cholesterol is deposited intracellularly. Cardiac allograft vasculopathy is less likely to calcify or develop collaterals than native coronary disease. The time for development of cardiac allograft vasculopathy also tends to be months to years rather than many years, which is the situation with native coronary artery disease.

Unfortunately cardiac allograft vasculopathy is quite common. Angiographically it occurs in nearly 50% of patients at 5 years, although the incidence of moderate and severe vasculopathy is much less, and only 7% of patients die or require re-transplantation at 5 years due to cardiac allograft vasculopathy (Figure 8.9). The prognosis of a patient with cardiac allograft vasculopathy is related to disease severity, and those with severe angiographic disease or severe intimal thickening on ultrasonography are more likely to suffer a cardiac event.

The precise etiology of cardiac allograft vasculopathy remains unclear, although immune mechanisms are involved because the disease affects the transplanted vessels (coronary arteries, coronary veins, donor segment of the aorta) whereas recipient vessels, even in patients who have undergone heterotopic

transplantation, are not affected. Alloimmune mechanisms and possibly immune changes after CMV infection play a role. Non-immune endothelial injury related to donor brain death, ischemia-reperfusion injury, direct injury from CMV infection in the donor or the recipient, and effects of immunosuppressive medications, particularly cyclosporine, may be contributing factors. Conventional risk factors in the donor and recipient may be risk factors for cardiac allograft vasculopathy. Donor characteristics shown to increase the risk of allograft vasculopathy include age, male gender, increased body mass index, hypertension, and pre-existing atherosclerosis (although donor lesions progress less rapidly than new lesions in the transplanted heart). Recipient characteristics shown to increase the risk of allograft vasculopathy include older age, male sex, black race, obesity, hyperlipidemia, hypertension, smoking, diabetes mellitus, and pretransplant diagnosis (although whether non-ischemic or ischemic disease increases risk varies in different studies).

Small studies have suggested factors which may prevent the onset or delay progression of allograft vasculopathy including treatment with aspirin, diltiazem, or angiotensin converting enzyme inhibitors; prophylaxis for CMV infection, and treatment of conventional risk factors. However, the clinical impact of such measures remains questionable. In a study of 40 cardiac transplant recipients randomized

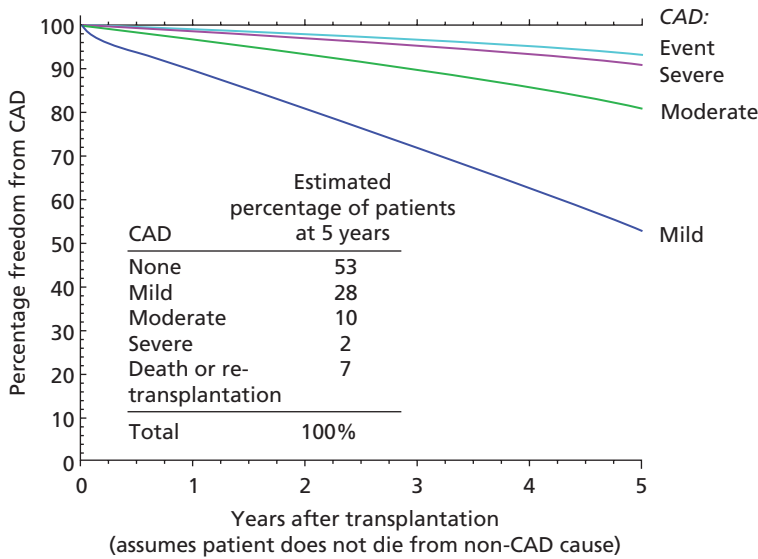


Figure 8.9 Freedom from mild, moderate, and severe cardiac allograft vasculopathy and events due to cardiac allograft vasculopathy as reported to the Cardiac Transplant Research Database: Jan 1990 to Dec 1994 – $n = 609$. CAD, coronary artery disease. (Reprinted with permission from Costanzo MR, Naftel DC, Pritzker MR, et al. Heart transplant coronary artery disease detected by coronary angiography: a multiinstitutional study of preoperative donor and recipient risk factors. *Cardiac Transplant Research Database. J Heart Lung Transplant* 1998;17:744–53.)

to vitamin C 500 mg plus vitamin E 400 IU twice daily versus placebo for 1 year, vitamin treatment prevented the increase in intimal index seen in the placebo group. No longer-term follow-up has been published. Further analysis of an MMF study also suggested a decrease in intimal proliferation with MMF versus azathioprine.

The first drug shown to decrease coronary intimal proliferation after cardiac transplantation was pravastatin. When patients were randomized to pravastatin versus placebo at transplantation, pravastatin not only decreased cholesterol, but also decreased the number of rejections with hemodynamic compromise, increased 1-year survival, and decreased the progression of cardiac allograft vasculopathy. A recent report confirmed increased survival and freedom from allograft vasculopathy and death in the pravastatin group after 10 years of follow-up. A similar benefit was shown with simvastatin. Of interest, an 8-year follow-up from the simvastatin study showed that patients who received placebo initially but began simvastatin at 4 years post-transplantation had an increased incidence of allograft vasculopathy compared with the group started on simvastatin at transplantation. Statins should therefore be routinely incorporated into the regimen of cardiac transplant recipients, starting at the time of transplantation. However, patients do require close follow-up of creatine kinase

levels and liver function tests as the adverse effects of statins are increased by drug interactions with the CNIs.

Studies using the TOR inhibitors, everolimus and sirolimus, instead of azathioprine from the time of cardiac transplantation have shown a decrease in cellular rejection and less progression of intimal thickness. These studies should, however, be interpreted cautiously because the data available reflect only the early post-transplant period, and everolimus and sirolimus increase serum lipids, particularly triglycerides, which could have long-term negative ramifications. Another limiting factor is that the comparator drug in the studies was azathioprine and not MMF, which may itself decrease progression of allograft vasculopathy. In addition, combined use of TOR inhibitors with cyclosporine was associated with increased serum creatinine concentrations, resulting in recommendations to decrease the target cyclosporine levels later in the studies. The increase in renal insufficiency produced by combined use of TOR inhibitors and cyclosporine is not yet understood.

Treatment for cardiac allograft vasculopathy is limited. As the disease is commonly diffuse and distal, percutaneous coronary interventions and bypass graft surgery are often not possible, and, when angioplasty is performed, re-stenosis is higher than in the general population (55% at 19 months in

the study by Halle et al. – see Further reading). In the small subset of patients who are candidates for bypass grafting, mortality is high. With the ability to stent coronary lesions, particularly using drug-eluting stents, outcomes of percutaneous coronary interventions in cardiac transplant recipients have improved; however, no large series have been published and long-term outcomes remain questionable. Attempts at percutaneous interventions or bypass surgery for allograft vasculopathy must be considered palliative and, in patients who are candidates for percutaneous coronary intervention or bypass surgery, distal angiographic disease predicts poor outcome.

An encouraging study randomized patients to sirolimus versus continuation of azathioprine or MMF when significant cardiac allograft vasculopathy was diagnosed. Patients randomized to sirolimus had fewer primary endpoints (death, angioplasty, bypass surgery, myocardial infarction, or an increase in angiographic coronary artery disease score) and secondary endpoints (cardiac hospitalizations, onset of heart failure, chest pain, and re-listing for transplantation) than the control group (Figure 8.10). Thus, many centers are initiating sirolimus in patients with cardiac allograft vasculopathy. However, whether the sirolimus should be substituted for the azathioprine or MMF as in the study or added to the immunosuppressive regimen is a question that remains unanswered.

The only true treatment for cardiac allograft vasculopathy is re-transplantation. However, survival after re-transplantation is decreased compared with that

after initial transplantation and, with the donor shortage, re-transplantation is done selectively (see “Re-transplantation”). Survival after re-transplantation for cardiac allograft vasculopathy is better than after re-transplantation for other indications, so in selected cases re-transplantation for allograft vasculopathy should be considered. Indeed, a recent series looking at re-transplantation for cardiac allograft vasculopathy found a 1-year survival rate of 85% for those re-transplanted between 1996 and 1999, approaching the outcome after initial transplantation. However, longer-term survival after re-transplantation is still compromised compared with that after initial transplantation.

Overview of medical complications following cardiac transplantation

Although medical complications after transplantation are detailed in Chapter 5, it is appropriate to discuss the importance of some complications in cardiac transplant recipients here. Table 8.5 shows causes of death at varying periods after cardiac transplantation in a recent era, excluding deaths due to technical factors, acute rejection, and primary and non-specific graft failure. In the first year, the primary cause of death is infection, whereas, later after transplantation, an increasing number of deaths are caused by malignancy and cardiac allograft vasculopathy.

Deaths due to renal failure also increase with time after cardiac transplantation. Risk factors for death due to infection early after cardiac transplantation include younger recipient age, male recipient, being

Figure 8.10 Freedom from clinical events (death, angioplasty, myocardial infarction or >25% increase in catheterization score) for patients with significant cardiac allograft vasculopathy treated with rapamycin versus control. (Reprinted with permission from Mancini D, Pinney S, Burkhoff D, et al. Use of sirolimus slows progression of cardiac transplantation vasculopathy. *Circulation* 2003;108:48–53.)

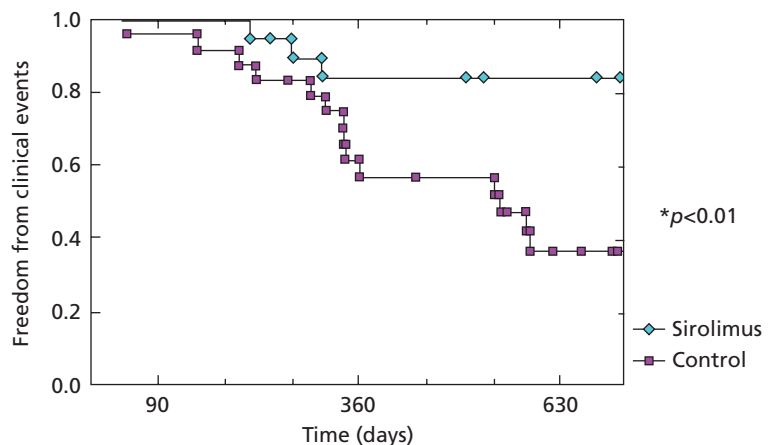


Table 8.5 Causes of death for adult heart transplant recipients (deaths January, 1992–June, 2003)^a

Cause of death	0–30 days (<i>n</i> = 2759)	31 days–1 year (<i>n</i> = 2310)	>1–3 years (<i>n</i> = 1737)	>3–5 years (<i>n</i> = 1492)	>5 years (<i>n</i> = 4009)
Infection	374 (13.5%)	813 (35.2%)	249 (14.4%)	148 (9.9%)	397 (9.9%)
Malignancy	4 (0.2%)	97 (4.1%)	258 (14.8%)	361 (24.2%)	964 (24.0%)
CAV	43 (1.6%)	111 (4.8%)	257 (14.8%)	268 (18.0%)	651 (16.2%)
Renal failure	17 (0.6%)	19 (0.8%)	31 (1.8%)	51 (3.4%)	238 (5.9%)
Other ^b	778 (28.2%)	525 (22.7%)	345 (19.9%)	298 (20%)	906 (22.7%)

^aExcluding deaths due to technical factors, acute rejection, primary failure, and graft failure.

^bIncluding multiorgan failure, pulmonary, cerebrovascular.

CAV, cardiac allograft vasculopathy. Reprinted with permission from Taylor DO, Edwards LB, Boucek MM, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-second official adult heart transplant report – 2005. *J Heart Lung Transplant* 2005;24:945–55 (and accompanying slide set).

on a ventilator at the time of transplantation, older donor age, and longer donor ischemic time. In long-term follow-up, older recipient age is the only significant risk factor for death from infection. Malignancy increases with time after cardiac transplantation, with non-skin malignancies affecting 5.6% of 5-year survivors and 6.5% of 7-year survivors. Chronic renal failure develops in nearly 11% of patients at 5 years after cardiac transplantation, with risk factors including age, preoperative renal function, postoperative acute renal failure, female recipient, hepatitis C infection, pretransplant hypertension, diabetes mellitus, and being transplanted more recently. Chronic renal insufficiency increases costs of care and the risk of death. As patients have a better outcome with renal transplantation than hemodialysis, and with the continued shortage of donor organs for the current renal waiting list, this becomes of societal importance. An area of active clinical investigation is defining means, particularly modifications in immunosuppression, to decrease the risk of renal failure after transplantation. Other significant morbidities that occur after cardiac transplantation and require ongoing medical attention are hypertension, hyperlipidemia, diabetes mellitus, obesity, and osteoporosis.

Prevention of complications after heart transplantation

Complications after heart transplantation challenge even the most experienced transplant physician.

Complications arise primarily from chronic immunosuppression, either directly or by worsening pre-existing conditions. Therefore it is incumbent to choose immunosuppressive regimens that prevent rejection but minimize side effects.

Key points 8.4 Avoiding medical complications after heart transplantation

- Preventing medical problems is vital, because problems are magnified in immunosuppressed patients
- Patients should participate in health maintenance by monitoring vital signs, recognizing and reporting symptoms, and adhering to a complex medical regimen
- Smoking is strongly discouraged; patients who resume smoking need referral to a smoking cessation program
- Regular aerobic exercise promotes physical rehabilitation and maintains functional capacity
- Maintaining ideal body weight is important, because obesity is associated with glucose intolerance and dyslipidemia

Prevention of infection

Transplant recipients are at life-long risk for infection. There is a peak of bacterial and viral infections in the first post-transplant month, followed by

a second peak of opportunistic infections (CMV, fungi, and protozoa) in the second to fifth months. Community-acquired infections are more common later. As the lung is the most commonly affected organ, chest radiographs are done routinely. Patients should report any fever or infectious symptoms immediately because infection can progress rapidly to death.

Prophylaxis decreases certain infections in heart transplant recipients. CMV is a common cause of infection, with donor-seropositive, recipient-seronegative (D+/R-) patients at highest risk. Two approaches to CMV prophylaxis are universal prophylaxis and pre-emptive therapy. Universal CMV prophylaxis for D+/R-, D-/R+, and D+/R+ heart transplant recipients involves valganciclovir for 3–6 months, sometimes with perioperative intravenous ganciclovir. Some centers add CMV Ig for D+/R- recipients. Pre-emptive therapy involves weekly monitoring to detect CMV viremia for the first 3 months. CMV viremia prompts treatment with intravenous ganciclovir or oral valganciclovir. Our institution uses universal prophylaxis.

Oral high-dose aciclovir and valaciclovir prevent reactivation of herpes simplex and herpes zoster. Trimethoprim-sulfamethoxazole, one single or double strength tablet daily for 1 year, prevents infection with *Pneumocystis jiroveci* (formerly *carinii*), *Toxoplasma gondii*, *Isospora belli*, and *Nocardia asteroides*. For pneumocystis prevention in patients allergic to sulfa, monthly inhaled pentamidine is an alternative.

Oral clotrimazole or nystatin (swish and swallow) prevents mucocutaneous candidiasis, although fluconazole or ketoconazole can be used. Patients need endocarditis prophylaxis before any dental, upper respiratory, gastrointestinal, or urologic procedures.

Patients should be immunized against hepatitis A, hepatitis B, pneumococcal pneumonia, influenza, diphtheria, and tetanus before transplantation. After transplantation, neither the patient nor any household contact should receive live viral vaccines, especially Sabin oral polio vaccine, because the virus is transmissible. Immunization with influenza vaccine after transplantation is controversial because of concerns about increased rejection. The transplant physician should be consulted before administration of any vaccine after transplantation.

Key points 8.5 Principles of prevention of infection after heart transplantation

As most infections are acquired by direct contact or inhalation, frequent hand washing with an antimicrobial soap and avoidance of crowded areas, tobacco smoke, construction sites, and exposure to people with respiratory illnesses are recommended

Food safety involves avoidance of unpasteurized, raw, or undercooked food, soft cheeses, and unpeeled vegetables and fruits

Patients should wash their hands thoroughly after contact with pets and should avoid animals with diarrhea, stray animals, reptiles, chicks, ducklings, cats aged <1 year, and monkeys

Sexually active patients should use latex condoms during sexual activity

Travel to developing countries involves substantial infectious risk and should be discussed with the transplant physician at least 2 months before departure

Prevention and detection of malignancy

There is a progressive linear increase in malignancies after transplantation, especially virally driven cancers. Cancer screening recommendations by the American Cancer Society include flexible sigmoidoscopy every 3–5 years starting at age 50, annual stool tests for occult blood, routine gynecologic examinations and mammography for women, and regular prostate examinations and prostate-specific antigen levels for men.

Surveillance for skin cancer and post transplant lymphoproliferative disorder (PTLD) are mandatory in transplant recipients. Sun protection and regular skin examinations are recommended. In a report from the Israel Penn International Transplant Tumor Registry, heart transplant patients had a higher incidence of PTLD and worse prognosis than other solid organ transplant recipients. An interesting finding in this series was that non-ischemic cardiomyopathy was the primary cardiac disease in 75% of patients who developed PTLD, representing a seven-fold increased risk compared with patients with ischemic or congenital heart disease. Increased surveillance and individualized immunosuppression may therefore be indicated for patients transplanted for cardiomyopathy.

The incidence of PTLD increases with the degree of immunosuppression. However, considerable interest exists in the possible antineoplastic activity of the TOR inhibitors, everolimus and sirolimus.

Hypertension and renal insufficiency

Hypertension induced by CNIs usually requires anti-hypertensive medication as well as salt restriction. Diuretics alone are rarely sufficient. ACE inhibitors and angiotensin receptor-blocking agents are effective antihypertensive agents, but hyperkalemia can be problematic and exacerbated by the CNIs. Diltiazem is associated with a lower incidence of allograft vasculopathy early after transplantation, but cyclosporine and tacrolimus levels are increased by diltiazem and need close monitoring. β Blockers should be used cautiously, particularly early after transplantation, because the denervated heart may rely on catecholamines to augment ventricular performance. Nephrotoxicity is associated with CNIs, so the lowest possible dose should be used to minimize renal dysfunction. Dehydration should be avoided because it potentiates renal toxicity.

Prevention and treatment of osteoporosis

About 50% of advanced heart failure patients have low bone mineral density due to a combination of vitamin D deficiency, low dietary calcium intake, loop diuretics, prerenal azotemia, immobilization, hepatic congestion, and hypogonadism. After transplantation, bone loss is accelerated by steroids and CNIs. Bone loss and fractures are highest in the first 3–12 months, ranging from 8% to 65%. Therefore, prevention of post-transplant osteoporosis begins before transplantation. All patients awaiting heart transplantation should be evaluated for bone mineral metabolism disorders and osteoporosis with bone densitometry, spine radiographs, and blood tests for calcium, vitamin D, PTH, thyroid function, and testosterone (males). All transplant candidates should receive 400–800 IU vitamin D and 1000–1500 mg elemental calcium daily. Patients with osteoporosis or osteopenia should also receive bisphosphonates. In patients with normal bone mineral density, pretransplant bisphosphonates should be considered immediately after transplantation. Bisphosphonates are renally excreted and cannot be used in patients with a serum creatinine >3.0 mg/dL or a creatinine clearance <30 mL/min.

Dyslipidemia

The adverse metabolic effects of immunosuppressive drugs, coupled with a genetic predisposition to hyperlipidemia and obesity, make dyslipidemia problematic after heart transplantation. Studies using HMG-CoA reductase inhibitors (statins) confirm the efficacy of pravastatin, simvastatin, and lovastatin in lowering cholesterol by 18–42%. In the Canadian Study of Cardiac Transplantation Atherosclerosis (CASCADE), patients receiving a statin had less allograft coronary disease and greater 5-year survival than patients on no statin therapy.

Statins have immunomodulatory effects independent of cholesterol lowering. These agents inhibit growth factor-induced cellular proliferation and cytokine activity. Statin use has been associated with a decreased risk of death from allograft failure in the first post-heart transplantation year, a decreased incidence of severe cellular rejection, and a reduction in ischemic events due to plaque rupture, possibly due to modulation of platelet thromboxane A_2 biosynthesis.

Aspirin

There are few data on aspirin use after heart transplantation, but most centers prescribe aspirin for primary and secondary prevention of cardiac allograft vasculopathy in doses ranging from 81 mg to 325 mg daily. Although allograft vasculopathy is primarily immunologically mediated, ischemic injury at the time of transplantation causes platelet activation, aggregation, and degranulation. After transplantation patients continue to exhibit marked platelet hyperaggregation. Evidence of platelet resistance to the inhibitory effects of aspirin in heart transplant recipients may explain the failure of antiplatelet agents to prevent myocardial infarction after heart transplantation.

Cardiac surgery, including re-transplantation, in heart transplant recipients

As the number of heart transplant recipients accumulates, the need for cardiac reoperations, including cardiac re-transplantation, has emerged. Cardiac allograft vasculopathy and tricuspid regurgitation are the

two major indications for cardiac surgery after cardiac transplantation.

Tricuspid regurgitation may result from endocarditis or biopsy-induced valve injury. Investigators at the Deutsches Herzzentrum Berlin, Germany, investigated 647 cardiac transplant recipients at their institution and identified tricuspid regurgitation in 20.1% (mild in 14.5%, moderate in 3.1%, and severe in 2.5%). Seventeen patients underwent valve repair or replacement. Tricuspid valve pathology revealed biopsy-induced rupture of the chordae tendineae at various valve segments, mostly the anterior and posterior leaflets. Ten patients (62.5%) were alive at 29.9 months (range 4–81 months) follow-up with nine survivors in NYHA classes I–II and one in class III. In their series, mild-to-moderate tricuspid regurgitation responded to medical therapy and was non-progressive without having a detrimental effect on right ventricular performance. Therefore, the need for tricuspid valve surgery must be carefully assessed.

As discussed under “Cardiac allograft vasculopathy,” the diffuse and distal nature of allograft vasculopathy precludes bypass surgery in many cases. In addition, mortality after bypass surgery for allograft vasculopathy is high, so its use in the treatment of allograft vasculopathy is palliative at best.

Early re-transplantation, especially within 6 months of primary cardiac transplantation, is associated with

poor results and is not recommended. As donor organ shortage remains a major issue in cardiac transplantation, and outcomes after re-transplantation are inferior to those after primary transplantation, indications for re-transplantation need to be carefully evaluated.

Most published data about cardiac re-transplantation are single center experiences. However, Srivastava et al. retrospectively analyzed 514 patients from the Joint ISHLT/UNOS Thoracic Registry who underwent cardiac re-transplantation between 1987 and 1998 (see Further reading). The predominant indications for re-transplantation were cardiac allograft vasculopathy (56%), primary graft failure (18%), and acute rejection (9%). Time from primary transplant to re-transplant ranged from 1 day to 15.5 years. One-year survival after re-transplantation as a function of time between first and re-transplantation is shown in Figure 8.11. Multivariate analysis determined that risk factors for mortality at 1 month after re-transplantation were center volume less than nine transplants/year, older recipient age, and the requirement for life support (VAD, ventilator, and /or inotropic therapy) and ICU care before re-transplantation. Recipient age and pretransplant mechanical ventilation continued to predict poor outcomes at 1 year. Re-transplantation performed more recently (1995 and after versus 1987–1994) positively affected outcome.

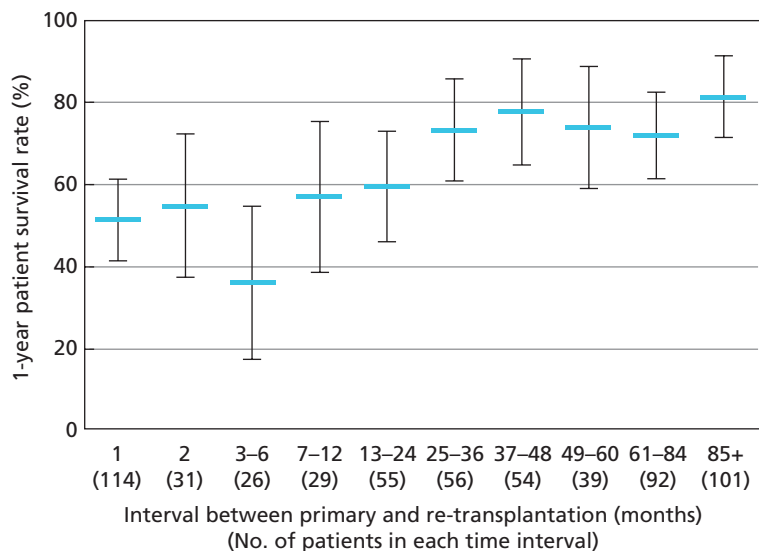


Figure 8.11 One-year survival after re-transplantation as a function of time between first transplant and re-transplantation. (Reprinted with permission from Srivastava R, Keck BM, Bennett LE, Hosenpud JD. The results of cardiac retransplantation: an analysis of the Joint International Society for Heart and Lung Transplantation/United Network for Organ Sharing Thoracic Registry. *Transplantation* 2000;70:606–12.)

Data from the ISHLT Registry show that, in 2003 and 2004, approximately 80 cardiac re-transplants were performed annually in North America, comprising 3–4% of all cardiac transplants. The 1-year survival rate in these patients reached 82.4% and the 3-year survival rate 71.6%, likely reflecting improved patient selection for re-transplantation.

Based on the above, selection criteria for re-transplantation at our institution (in addition to those defined for primary transplant) are as follows:

Indications

1. Diffuse cardiac allograft vasculopathy not amenable to angioplasty/stenting or bypass surgery, especially with associated LV dysfunction.
2. Graft failure from suboptimal donor or acute or chronic rejection, with symptomatic, progressive heart failure.

Contraindications

1. Graft failure for any reason within 2 weeks of transplantation
2. Graft failure within 6 months of transplantation if associated with acute rejection and hemodynamic compromise
3. Patient age >55 years
4. PTLD, if disease free for less than 5 years
5. Patient non-compliance.

Case: re-transplantation

A 48-year-old man is now 15 years after heart transplantation for non-ischemic cardiomyopathy. He had two rejection episodes that were successfully treated in the first postoperative year but otherwise did well. Three years ago at his annual cardiac catheterization, he was noted to have an 80% lesion in his LAD, which was successfully stented. Over the next 2 years, catheterizations have shown that his LAD stent remains patent but he has developed diffuse, progressive, allograft vasculopathy with a gradual decline in his LVEF to 25% and he now has symptomatic heart failure. He has been very compliant with his medical regimen, his creatinine is 1.5mg/dL, and he has no contraindications to re-transplantation. What would you do?

The future of cardiac transplantation

Outcomes after cardiac transplantation have improved considerably since Dr Barnard performed the first heart transplantation in 1967. However, survival is

still limited by deaths due to rejection, cardiac allograft vasculopathy, and complications of immunosuppression. The donor shortage also limits the number of heart transplantations performed. Improved outcomes after heart transplantation are critically dependent on more specific/targeted methods of immunosuppression, which can further decrease immunologic deaths without increasing morbidity and mortality due to complications of immunosuppression. Better utilization of available donor hearts, facilitated by improved donor management, is also critical.

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