CHAPTER 91 HEART TRANSPLANTATION

CHARLES W. HOOPES

Cardiac allotransplantation is now an established therapeutic modality for end-stage heart disease (1). Although the operative procedure remains essentially unchanged, recent advances in mechanical assist technology and significant advances in the medical therapy of congestive heart failure have changed heart transplantation from an “operation” to a definitive therapy among competing therapies in integrated heart failure management programs. Ventricular assist devices (VAD), cardiac resynchronization therapy, nontransplant surgical procedures, and novel molecular strategies have further complicated the process of patient selection for transplantation. This discussion will review the current status of clinical cardiac transplantation, describe the diagnostic algorithms of the acute decompensated heart failure patient that determine appropriate patient selection for cardiac transplantation, and identify the major perioperative risk factors for acute allograft loss and the clinical strategies designed to attenuate these risks.

CARDIAC TRANSPLANTATION: CURRENT STATUS

Registry data from the International Society of Heart and Lung Transplantation demonstrate continued improvement in clinical outcomes with the current expected half life (50% survival) of cardiac allografts at 10 years (2). Conditional half life for patients surviving to 1 year now exceeds 13 years. Indications for transplantation continue to be equally divided between patients with ischemic cardiomyopathy and those with nonischemic dilated cardiomyopathy, and among recent transplant recipients, 40% were receiving inotropic support and 30% were on some form of mechanical circulatory device. However, fewer than half of all patients between 2001 and 2004 were hospitalized at the time of transplant versus a nearly 70% hospitalization rate between 1999 and 2001 (2).

Categoric risk factors for early mortality are essentially unchanged (2). Requirement for dialysis at the time of transplant, female organ recipient, donor with a cerebrovascular accident as cause of death, coronary artery disease as the indication for transplantation, and the timing of transplant are routinely used to determine candidacy for transplantation (4). The currently accepted indication for transplantation is that the patient selection for cardiac transplantation, and identify the major perioperative risk factors for acute allograft loss and the clinical strategies designed to attenuate these risks.

Late morbidity after transplantation continues to be defined by increasing renal dysfunction, progressive hyperlipidemia, and diabetes, with nearly 10% of all heart recipients having significant renal insufficiency (creatinine >3.5) by 8 years and an additional 5% requiring long-term dialysis (2). Coronary artery vasculopathy (CAV) and malignancy continue to impact late mortality with the incidence of any malignancy approaching 35% at 10 years. By 10 years, only 44% of patients are free of angiographic CAV. Donor hypertension and early infection (within 2 weeks of transplant) are independent categoric risk factors for coronary artery vasculopathy whereas donor age and elevated recipient body mass index are continuous variables contributing to progressive CAV. This is consistent with our institutional bias that the biology of CAV is an inherent characteristic of allograft selection and early inflammatory injury. Skin cancer is the most common malignancy among solid organ transplant recipients and complicates the care in 21% of heart patients by 10 years (2).

PATIENT SELECTION AND ORGAN ALLOCATION

Hemodynamic Markers of Heart Failure

The decision to transplant should be determined by the natural history of underlying disease, the relative efficacy of medical therapy, and the patient’s perception of quality of life. Although the objective hemodynamic criteria used to define end stage heart disease have not changed significantly in the past decade, the clinical profile of patients who die from heart failure is radically different (3). Knowing the risk of dying and the prognosis of patients receiving optimal medical therapy is critical to the determination of transplant candidacy and timing. Here we discuss the objective criteria of oxygen consumption (VO_2) and right heart catheterization that define the hemodynamics of transplant candidacy, discuss the evolving concept of the circulatory-renal limit (CRL) in predicting medical efficacy and the timing of transplant, describe the Heart Failure Survival Score (HFSS), and integrate these issues into the current paradigm of organ allocation. This discussion is focused on the ambulatory patient with acute decompensated heart failure.

Cardiopulmonary testing as a measure of oxygen consumption is routinely used to determine candidacy for transplantation (4). The currently accepted indication for transplantation is a peak VO_2 <10 mL/kg per minute in patients with adequate β-blockade who achieved anaerobic threshold. Patients with a VO_2 between 10 and 14 mL/kg per minute are more problematic, and decisions to list for transplantation should be individualized. The use of VO_2 as a discriminatory variable requires...
experience and attention to detail in testing performance. It is important to note that patients tolerating \( \beta \)-blockade demonstrated improved survival with equivalent \( V_O^2 \). It is also notable that appropriate patient selection assumes maximal effort to achieve a plateau of performance. In populations with limited functional status as a respiratory exchange ratio (RER) > 1.05 is generally considered a maximal exercise test. Peak \( V_O^2 \) also varies with age and gender and is normalized for body weight with heavier patients having a lower \( V_O^2 \) at comparable levels of performance. In the era prior to widespread use of \( \beta \)-blockers and angiotensin-converting enzyme (ACE) inhibitors, a \( V_O^2 \) maximum of < 50% was shown to be a significant predictor of cardiac death. Nonetheless, isolated peak \( V_O^2 \) should not be used as the sole criterion for transplant eligibility.

Right heart catheterization provides information on cardiac output, ventricular filling pressures, and pulmonary vascular resistance (PVR) and is an absolute prerequisite to consideration for transplantation (4-6). A pulmonary vascular resistance greater than 5 Wood units, an indexed PVR greater than 6 Wood units or a transpulmonary gradient (TPG) greater than 16 to 20 mm Hg have been considered relative contraindications to transplant (1 Wood Unit = 80 dynes - cm\(^{-2}\)). Candidacy for transplantation is less dependent on the absolute measures of PVR than on the responsiveness of the pulmonary vascular bed to therapy. Heart failure patients with pulmonary artery (PA) systolic pressures greater than 50 mm Hg and either a PVR > 3 Wood units or a TPG > 15 mm Hg are routinely challenged with multiple vasodilators to ascertain whether the elevated pulmonary pressures are reactive. Most patients with acute decompensated heart failure have elevated left-sided filling pressures with secondary pulmonary hypertension. Pharmacologically unloading the left ventricle with sodium nitroprusside while maintaining a systolic blood pressure (SBP) of > 85 mm Hg is generally considered evidence of a reactive vascular bed and does not preclude transplantation.

A significant minority of patients have evidence of fixed pulmonary hypertension. It is our institutional practice to initially evaluate patients who fail provocative vasodilatory testing for an anatomic substrate of pulmonary hypertension including chronic thromboembolic disease, pulmonary parenchymal disease, or history of significant sleep apnea. Patients without evidence of an anatomic substrate are treated with aggressive diuretics and short-term inotropy with the phosphodiesterase inhibitor milrinone. If subsequent provocative testing demonstrates continued nonreactivity, dobutamine is added to the inotropic support for synergy. Such vasodilatory conditioning generally improves pulmonary vascular resistance, but these patients remain at higher risk for acute cardiac death prior to transplant (7) and in our experience remain at significant risk for elevated PA pressures after transplantation. It is important to recognize that the reversibility of PVR in patients with low left ventricular ejection fraction (LVEF) cannot be assessed without unloading the left ventricle. Fixed pulmonary hypertension has been effectively treated with mechanical circulatory support allowing isolated cardiac transplantation in patients initially thought to require a combined heart-lung procedure (8).

Renal dysfunction is among the most significant clinical variables complicating the decision to transplant and one of the most significant morbidities after transplant (2). A serum creatinine > 2 mg/dL or a creatinine clearance (CrCl) < 30 mL/minute were initially considered evidence of irreversible renal dysfunction and a contraindication to transplant (4). Current practice patterns are variable and institution specific, but efficient arteriolar vasodilation mediated by elevated angiotensin (ACE) inhibitors and angiotensin-converting enzyme (ACE) inhibitors with resultant interstitial fibrosis and glomerular scarring is a common feature of progressive heart failure. We do not consider renal dysfunction a contraindication to transplant and have actively pursued combined heart and kidney transplant in patients at high risk for end-stage renal disease in the early postoperative interval. Outcomes for combined transplant are comparable to those of isolated cardiac allografts (9). Regardless of approach, the decision to exclude patient candidacy secondary to significant renal dysfunction or to simultaneously transplant a renal allograft requires careful consideration of the cause of preoperative renal insufficiency, the degree to which renal insufficiency is irreversible, and the probability of progressive renal failure after transplant.

There is little disagreement that a CrCl > 80 mL/minute corrected for body surface area and a urine protein > 150 mg per 24 hours present no significant risk for transplant. Elevated creatinine is a common manifestation of decompensated heart failure and even mild increases are associated with poor outcome (2). It is our practice to routinely evaluate any potential recipient with an elevated creatinine (> 1.5 mg/dL) or questionable CrCl by estimated glomerular filtration rate (eGFR) using the risk stratified database and analysis of the Modification of Diet in Renal Disease (MDRD) study (http://nephron.com/cgi-bin/mdrd.cgi). Patients with decreased GFR or marginal GFR in the context of associated proteinuria are referred to transplant nephrology for formal evaluation and consideration as to candidacy for combined organ transplant. Renal ultrasound is routinely used to assess for acute renal disease and biopsy is necessary for renovascular disease, and sequential biopsy may be necessary to determine renal transplant candidacy in the context of progressive heart failure (10). The decision to offer combined heart-kidney transplant remains controversial as the heart recipient removes a renal allograft from the kidney donor pool. Alternatively, transplantation in patients with poorly characterized renal dysfunction carries significant morbidity with nearly 20% of heart recipients demonstrating renal insufficiency by 5 years (2).

### Neurohormonal Markers of Heart Failure

The natural history of heart failure is characterized by systemic neurohormonal activation in response to the structural and functional remodeling of decreased ejection fraction and progressive volume overload. Optimal medical therapy of heart failure is designed to ameliorate these neurohormonal changes—\( \beta \)-blockade of adrenergic pathways, diuretics to reduce volume overload and natriuretic hormone production, and various inhibitors of the renin-angiotensin system including ACE inhibitors and angiotensin receptor blockade. Although there is as yet no composite score of multiple neurohormonal markers to describe the dynamic changes in heart failure, there are a number of relationships between various markers and cardiac remodeling that allow risk stratification of patients considered for transplant. Analysis of the RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) trial data demonstrated that temporal increases in brain natriuretic (BNP) and N-terminal atrial natriuretic peptide (NT-ANP) during medical therapy were associated with...
concurrent reductions in ejection fraction and increases in end-diastolic and systolic volume (11). In a multivariate analysis of that same data set, NT-ANP and norepinephrine increases over time and beyond baseline were independently predictive of an increased risk for death and heart failure hospitalization. We use NT-ANP as a marker to evaluate the adequacy and response to acute heart failure therapy and consider it a physiologic marker of volume overload. C-reactive protein (CRP), a nonspecific marker of inflammation, is considered a sensitive marker of the neurohormonal milieu in acute heart failure and a more sensitive marker of prognosis. In patients with decompensated heart failure, CRP is most elevated (CRP > 15%–18 mg%) and associated with poor outcomes regardless of ejection fraction (12).

Neurohormonal modulation with nonselective β-blockers, ACE inhibitors, angiotensin receptor blockade, and aldosterone antagonists directly influences patient survival and constitutes the basis for contemporary heart failure therapy. However, the survival advantage of effective early therapy and the prevention of sudden death has created a population of patients very different from that of previous decades. The decision to recommend definitive therapy, whether transplant or mechanical ventricular assist, is contingent on the ability to identify which patients can tolerate aggressive therapy. Intolerance to such medical therapy defines a high-risk population of heart failure patients at risk for early death and has led to the important concept of the circulatory-renal limit (13).

Systemic blood pressure, renal perfusion, and sodium homeostasis are controlled by the renin–angiotensin–aldosterone system via angiotensin-II–mediated vasoconstriction of the peripheral and efferent renal arterioles. Vasoconstriction potentiates the sympathetic stimulation of the adrenergic pathways, and serum sodium indirectly influences volume status by influencing intravascular oncotic pressure. Symptomatic hypotension, renal dysfunction, and hyperkalemia define the circulatory-renal limit and identify patients unable to tolerate escalating levels of β-blockade and ACE inhibition. Among ACE inhibitor-intolerant patients, mortality is greater than 50% by 6 months, and patients requiring inotropic support to maintain systemic blood pressure and renal perfusion have even poorer prognosis with no survivors by 4 months (13).

**TABLE 91.1**

<table>
<thead>
<tr>
<th>HEART FAILURE SURVIVAL SCORE (HFSS)</th>
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<tbody>
<tr>
<td>Coronary artery disease</td>
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<tr>
<td>(yes = 1, no = 0)</td>
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<tr>
<td>(yes = 1, no = 0)</td>
</tr>
<tr>
<td>Intraventricular conduction delay</td>
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<tr>
<td>(yes = 1, no = 0)</td>
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<tr>
<td>Left ventricular ejection fraction (%)</td>
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<td>(yes = 1, no = 0)</td>
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<tr>
<td>Sodium concentration (mmol/L)</td>
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<td>(yes = 1, no = 0)</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
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<td>(yes = 1, no = 0)</td>
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<tr>
<td>Peak VO2 (ml/kg/min)</td>
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<tr>
<td>(yes = 1, no = 0)</td>
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<td>HFSS = . . . . . . . . . .</td>
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Failure National Registry (ADHERE) demonstrates that blood urea nitrogen (BUN) >43 mg/dL at admission is the best discriminator between hospital survivors and nonsurvivors, followed by a systolic blood pressure <115 mm Hg and a creatinine >2.75 mg/dL. In-hospital mortality for the high-risk group (elevated BUN and creatinine, low SBP) is approximately 23% (18).

It is our institutional bias that the decision to transplant is individualized and directed toward patient-specific quality of life. Hemodynamic and objective measures of cardiac performance are always used to make transplant decisions, but functional status, a history of acute decompensation, neurohormonal markers of compensated heart failure, and intolerance to optimal medical therapy influence the thought process and timing of decisions. We do not question that transplantation improves cardiac function but always question whether “fixing the heart” will significantly improve the patient. While individual physicians advocate for patients, the decision to transplant is collective and represents the balance of interest between responsible use of a shared limited resource and appropriate patient need. Heart transplantation as an operation should not exist outside an integrated heart failure service and an active mechanical circulatory assist program. We do not consider decompensated heart failure an indication for transplantation. Every effort is made to establish a euvolemic state with adequate end organ perfusion before proceeding to transplantation. Patients intolerant of maximal medical therapy are referred for ventricular device placement, and patients with acute cardiogenic shock refractory to medical therapy are stabilized with extracorporeal life support (ECLS) before placement of definitive ventricular assist devices and consideration for transplantation. The separation of mechanical ventricular assist technology and transplantation in this discussion is editorial and does not reflect current thinking in the surgical management of end-stage heart disease.

Organ Allocation

The current allocation system for donor hearts is designed to prioritize patients with the most urgent medical need of transplantation—potential recipients with mechanical circulatory assist devices and patients requiring multiple inotropes or a single high-dose inotrope (dopaminne >7.5 μg/kg per minute or milrinone >0.5 μg/kg per minute) are listed as status 1A. Patients requiring a single continuous low-dose inotrope to maintain hemodynamics and end organ perfusion are listed as 1B. Patients with end-stage heart disease who fail to meet either of these criteria are listed as status 2. Because of the increasing efficacy of medical therapy, the survival benefit of transplantation to United Network for Organ Sharing (UNOS) status 2 patients has been questioned (19). As a result, hearts are now offered to local 1A and 1B recipients and subsequently offered to regional 1A and 1B recipients within 500 miles of a donor hospital before returning to the local transplant centers for UNOS status 2 patients. There have been serious suggestions that heart transplantation be subjected to a randomized trial against medical therapy for patients currently listed as UNOS status 2.

One consequence of regional allocation beyond the local organ procurement organization is the logistic difficulty of cross-matching hearts to allosensitized patients. Nearly 20% of potential recipients in our program have significant anti-HLA antibodies or panel reactive antibody (PRA) >10%. Because of the logistic difficulty of maintaining potential recipient sera at all possible donor centers, we have come to rely on the virtual cross-match to exclude organs at significant risk for acute immune mediated rejection (20). Currently, all potential recipients are screened for class I and class II anti-HLA IgG antibodies by flow cytometry. IFHLA alloantibodies are detected, the specificity of the HLA antibody is determined by single HLA molecule high-definition reagents. A list of exclusive antigens is used to virtually cross-match and exclude organs with potentially cross-reactive allospecific HLAs. Local donors are prospectively cross-matched using cell based, complement-dependent cytotoxicity assays to identify immunoreactive allografts. It is important to recognize that cytotoxicity assays are subjective and open to significant differences in interpretation, particularly at lower levels of reactivity. Infection and transfusion are the most frequent source of alloreactive antibodies in potential organ recipients and as such should be carefully noted in the critical care environment. It is our practice to screen actively listed potential transplant recipients every 30 days for alloreactive antibodies.

ACUTE ALLOGRAFT LOSS

Within 30 days of transplantation, causes of death include graft failure (primary and nonspecific) accounting for 40%, multorgan system failure (14%), and noncytomegalovirus (non-CMV) infection (13%). Here we discuss the cause and management of primary graft loss focusing on the mechanisms of acute right ventricular failure, acute immune injury in the context of current practices of immunosuppression and induction therapy, and the biology of opportunistic infections in the early posttransplant period.

Right Ventricular Dysfunction and Allograft Failure

Whereas acute right ventricular (RV) failure at the time of allograft implantation is rare but highly morbid condition with historical mortalities approaching 50% to 30%, RV dysfunction after allograft implantation is common. Nearly 20% of orthotopic heart transplants demonstrate some degree of RV dysfunction as manifested by tricuspid regurgitation. Tricuspid regurgitation has recently been shown to be a predictor of late survival after cardiac transplantation, suggesting that early RV dysfunction is a marker of poor outcome (21). The etiology of transplant RV dysfunction is poorly understood but clearly multifactorial and includes primary aspects of donor organ biology (e.g., primary right ventricular graft dysfunction), inherent injury secondary to the procurement process (e.g., ischemia-reperfusion injury), and specific characteristics of recipient pathophysiology (e.g., elevated pulmonary vascular resistance).

Heart donors with cerebrovascular accident as the cause of death have consistently demonstrated a significant negative impact on 1-year posttransplant mortality (2), and experimental data have supported the concept that donor brain death contributes to right ventricular dysfunction after cardiac
transplantation. Animal studies have demonstrated a significant decrease in right ventricular function after transplantation in hearts retrieved from a brain dead donor whereas right ventricular function is maintained or increased after implantation of normal hearts even in recipients with chronic pulmonary hypertension (22). Furthermore, large animal models assessing the intrinsic myocardial mechanics of transplanted hearts independent of the severe changes in peripheral loading conditions that accompany the catecholamine storm of brain death (elevated peripheral and pulmonary vascular resistance) demonstrate a nearly 40\% reduction in RV contractility with- out a similar decrease in LV contractility (22). This suggests that RV dysfunction is primarily related to the status of the donor heart, and although elevated pulmonary vascular resistance will increase the severity of postoperative RV dysfunction, it is unlikely that elevated PVR independently creates RV dysfunction.

The early biology of transplanted hearts is defined by denervation and diastolic dysfunction. Loss of afferent parasympathetic vagal tone and corresponding lowering of myocardial catecholamine levels in response to sympathetic denervation results in higher resting heart rates and a blunted response to hypovolemia and decreased preload. A poorly understood but useful consequence of denervation is increased presynaptic sensitivity to \( \beta \)-adrenergic stimulation (22). The transplanted heart is also "stiff," and restrictive physiology is expected in the immediate postoperative period. Elevated diastolic ventricular filling pressures generally diminish within weeks of transplant, but persistent diastolic dysfunction may represent donor-recipient size mismatch, myocardial injury from harvest ischemia, intrinsic characteristics of the donor heart (e.g., hypertrophy), or evidence of rejection. Because of limited therapies, prophylaxis for acute allograft dysfunction is a preferable clinical strategy. It is our practice to start inhaled nitric oxide (NO) (20 ppm) prior to weaning from cardiopulmonary bypass to lower pulmonary vascular resistance in patients with preoperative PVR \( \geq 3 \) Wood units. All patients exit the operative theatre on low- to moderate-dose epinephrine (0.02–0.06 \( \mu \)g/kg per minute) and patients receiving chronic afterload reduction preoperatively (e.g., intravenous milrinone) are simultaneously started on low-dose inhaled nitric oxide (NO) (0.02–0.04 \( \mu \)g/kg per minute). Patients are atrially paced (92 beats per minute [bpm]), or AV sequentially paced, in the immediate postoperative period. In the absence of significant tricuspid regurgitation and RV dysfunction, NO is weaned in the immediate postoperative period, and patients are generally weaned from NO within 6 hours of exiting the operating room (OR). Caution should be used in weaning NO as rebound pulmonary hypertension has been observed (23). We have not found this to be a significant clinical problem outside the pediatric population. Inotropic support is maintained for the initial 24 hours and weaned off between 24 and 36 hours as determined by clinical exam.

We routinely start milrinone (0.2–0.5 \( \mu \)g/kg per minute) as a selective pulmonary vasodilator and for peripheral afterload reduction between 12 and 24 hours postoperatively as epinephrine/norepinephrine are withdrawn. Patients frequently remain on low-dose milrinone (0.2 \( \mu \)g/kg per minute) for 3 to 5 days after transplant. Approximately half of our patients have right heart catheters postoperatively. We have found clinical exam and echocardiogram effective for evaluating ventricular function, filling pressures, and RV strain, and right heart catheters are generally placed for specific diagnostic questions and rarely guide clinical management. All patients undergo right heart catheterization and biopsy within 7 to 14 days of transplant. For patients with biventricular dysfunction thought secondary to reperfusion injury, we have anecdotally found the combination of epinephrine and low-dose calcium (50–200 mg/hour) efficacious in the postoperative period. This is consistent with theoretical models identifying calcium homeostasis as a significant pathway in ischemia–reperfusion injury (23).

**Ischemia–reperfusion Injury**

Over the past three decades, studies of ischemia–reperfusion injury have created an enormous amount of descriptive data, a limited amount of information, and a small amount of integrated knowledge. Traditional views hold that the obligatory ischemia of organ procurement induces endothelial dysfunction, lipid peroxidation with loss of membrane integrity, free radical superoxide production, dysregulation of intracellular and mitochondrial calcium flux, and neutrophil activation with allograft infiltration. Reperfusion at the time of allograft implantation is thought to extend the inflammatory injury with subsequent apoptosis and delayed cell death contributing to graft dysfunction. The volume of translational research directed at the cause of ischemia–reperfusion injury and the efforts to design surgical strategies to diminish its impact on the vascular biology of solid organ transplants precludes any significant discussion, and the subject has been recently reviewed (23). However, two conceptual shifts of probable impact on the treatment and understanding of acute cardiac allograft function in the context ischemia–reperfusion injury deserve mention.

First, reintroduction of blood flow to the thoracic aorta in a stutering fashion has had widespread application among transplant surgeons. This is based on anecdotal observations that slow and intermittent reperfusion limits clinical reperfusion injury. Similar patterns of postconditioning that have recently been demonstrated to reduce reperfusion injury and enhance myocardial function in patients experiencing acute myocardial infarcts (24). The mechanism of postconditioning appears to involve release of endogenous adenosine and opioid receptor ligands (24). A second observation is the increasing appreciation of toll-like receptors in ischemia–reperfusion injury. Toll-like receptors, one class of the pathogen recognition system involved in innate immunity, have been associated with early cytokine release after reperfusion (23). It is likely that antagonists of both systems will eventually find application in modulating the adhesion molecule engagement and proinflammatory cytokine biology of allograft reperfusion injury.

**Rejection and Immunosuppression**

With the exception of homozygous twins, all allografts are incompatible. This incompatibility is defined by the predominant mechanism of allogrognition—humoral or cellular—and the temporal pattern of allograft rejection. Hyperacute rejection occurs within minutes to hours of allograft reperfusion and is a rare form of perioperative graft loss caused by preformed antibodies directed against donor HLA or endothelial antigen. Complement activation results in intravascular...
thrombosis and ischemic graft dysfunction. There is no med-
ical therapy as graft loss is nearly immediate and salvage re-
quires mechanical circulatory support (ECLS or VAD) and con-
sideration for retransplantation. Diagnosis is mandatory and
should be directed at confirming AB0 compatibility and iden-
tifying the antibody-specific alloantigen. Although the UNOS
ethics committee recognizes retransplantation as a therapeu-
tic option, it also notes that “graft failure, particularly early or
immediate failure, evokes significant concerns regarding repeat
 transplantation” and suggests that “the likelihood of long-term
survival of a repeat transplant should receive strong considera-
tion” (www.UNOS.org/bioethics). Histologic confirmation of
humoral injury requires immunostains for complement (C4d),
immunoglobulins, and macrophages (CD68) within capillaries.

Acute rejection is historically considered a T-cell–mediated
process with perivascular infiltration of lymphocytes and
macrophages and variable degrees of myonecrosis. It can occur
anytime after transplantation but is most commonly diagnosed
within the first 6 months—nearly 60% of heart recipients—and
is the most common form of rejection within days to weeks after
allograft implantation (25). The diagnosis and manage-
ment of acute rejection can be problematic. Early ischemic in-
jury can manifest as significant myocyte injury with various
degrees of inflammation. Although mild acute cellular rejec-
tion (grade 1R) with perivascular mononuclear cells and se-
vere acute cellular rejection (grade 3R) with diffuse mononu-
clear cell infiltrates and extensive myonecrosis are easily dis-
tinguished from ischemic injury, moderate rejection requires
interpretation. Perivascular and interstitial mononuclear cells
predominate with few (two or more) foci of myocyte injury in
moderate acute cellular rejection. A predominance of neutro-
phils and organ dysfunction may suggest the possibility of
a humoral component (26).

Chronic rejection is characterized by circumferential my-
ointimal proliferation and progressive coronary artery vascu-
lopathy. Nearly half of all heart transplants demonstrate angio-
graphically recognizable CAV by year five. Early acute vascular
rejection, inadequately treated acute rejection, CMV infection,
non-CMV infection, donor age, and donor hypertension are
among the factors associated with the biology of chronic re-
 jection, and early CAV (occurring within 1 year) contributes
to significant increases in mortality when compared to patients
without CAV (27).

The goal of early biopsy is diagnosis, and the subsequent histology
must be interpreted within the patient-specific clini-
cal context. This clinical context requires active participation
of both surgeon and cardiologist with the reviewing patholo-
gist, and it is our policy to collectively review all biopsy spec-
imens. Interobserver differences in the interpretation of biop-
sies can be significant, and there is an understandable tendency
to “overcall” inflammation and overtreat mild rejection be-
cause of the fear of rejection; overimmunosuppression in the
acute postoperative phase can result in catastrophic infection
whereas failure to adequately treat rejection can result in sig-
ificant allograft injury. We do not treat mild rejection (grade 1R).
Severe rejection (grade 3R) is always treated with pulse
steroids and antilymphocyte therapy, and in the context of or-
gan dysfunction, every attempt is made to rule out humoral
rejection. If circulating antibody is detected, patients undergo
plasmapheresis although this is uncommon in our practice since
all recipients undergo retrospective cross-match to guide post-
transplant management. Moderate rejection can be confused
with ischemic injury, and we routinely treat grade 2R biopsies
with pulse steroids and rebiopsy within 7 to 10 days.

Balanced Risk: Immunosuppression
and Infection

Coronary artery vasculopathy is a probable complication of
underimmunosuppression whereas early infection and late ma-
lagniﬁcations are probable complications of overimmunosuppres-
sion. These opposing problems represent the major failure
of contemporary thoracic transplantation. Immunosuppressive
therapies remain institution specific. Drug protocols for tho-
racic transplant are derived largely from the investigational
experiences of renal transplant, and monitoring of immuno-
 suppressive drug therapy is based on pharmacology and presumed
therapeutic drug levels rather than the analysis of specific mea-
sures of general and donor-specific immune responsiveness.
Nonetheless, there are shared immunosuppressive strategies for
the induction of immune tolerance at the time of allograft im-
plantation and for the maintenance of chronic immune sup-
pression over time. Rescue (antirejection) therapy in response
to histologic rejection remains very problematic as there is no
direct relationship between microscopic evidence of allograft
rejection, allograft dysfunction, and patient survival. Acute re-
 jection, outside the context of patient noncompliance or unap-
 preciated preformed antibody in the sensitized organ recipient,
is uncommon and accounts for only 2% of deaths at 1 year
(Fig. 91.1).

Induction Therapy and Maintenance
Immunosuppression

The goal of induction therapy is clonal deletion of T cells with
allograft-specific antigen recognition. The reality of induction
therapy is generalized T-cell anergy with effective immuno-
 suppression at the risk of generalized immunodeficiency. Although
the efficacy of induction therapy in cardiac transplantation re-
mains controversial and is necessarily balanced against the risk
of increased infection, approximately half of all heart trans-
plant patients receive antilymphocyte induction therapy at the
time of allograft implantation (2). Collective registry data sug-
gest no significant differences in survival among patients re-
ceiving induction therapy. However, the specific risk profiles
for various induction therapies—nonspecific polyclonals ver-
sus specific monoclonals—are distinct, and the application of
various induction therapies is often patient specific.

Polyclonal antilymphocyte antibody preparations are
 gamma globulin fractions of serum derived from animals
immunized with human lymphoid tissue—rabbit-derived an-
tilymphocyte/thymocyte globulin (ALG, Thymoglobulin) or
horse-derived antithymocyte globulin (ATG). Both prepara-
tions bind various cell surface antigens on B and T cells
with subsequent complement-mediated cytolyis and eventual
opsonization (28). Therapy is nonspecific, and cross-reactivity
may induce leukopenia and thrombocytopenia. The current
polyclonals are foreign proteins and induce immune re-
response in the organ recipient; this limits long-term efficacy
FIGURE 91.1. Causes of specific mortality in heart transplantation. Note the early incidence of infection and graft failure followed by a dose-dependent rise in coronary artery vasculopathy (CAV) and malignancy.


Without recurrent therapy and raises concerns as to the potential for hypersensitivity responses with subsequent exposures. Cytokine release syndrome complicates polyclonal therapy in approximately 20% of patients, and serum sickness has been reported with equine-derived antithymocyte globulin. Nonetheless, while very limited retrospective reviews suggest some efficacy to polyclonal induction therapy (29,30) the practice and experience remains largely institution specific.

Induction therapy with the monoclonal antibody daclizumab (Zenapax), directed against the interleukin-2 receptor, is now widespread among cardiac transplant programs. A randomized trial of daclizumab as induction therapy demonstrated a decreased rate of acute cellular rejection (25% vs. 41%) and an increased median time to the primary end points of histologic rejection, allograft dysfunction, retransplantation, or death (31). However, the mortality in the daclizumab group was 6.5% at 6 months versus 3.2% in the nontreatment group with most of the treatment group deaths secondary to infection in patients receiving a second antilymphocyte cytolytic therapy (32). The efficacy of daclizumab may be influenced by the degree of donor-recipient mismatch at the HLA-DR histocompatibility locus (33).

It is our institutional practice to use the humanized antitumor necrosis factor-alpha (TNF-α) antibody infliximab (Remicade) to prevent potential nephrotoxicity in the perioperative setting. Patients receive 1 mg/kg intravenously (IV) at the time of transplant with an additional dose given on postoperative day 7 and every 14 days thereafter for a total of three to five cumulative doses. In reality, only 20% of patients receive the full five doses with therapy curtailed in response to leukopenia or two consecutive biopsies with no evidence of rejection in the context of well-tolerated therapeutic levels of calcineurin inhibitor. As an alternative induction therapy, basiliximab (Simulect), a chimeric anti-IL-2 receptor monoclonal antibody, is given on induction (20 mg IV) and postoperative day 4 (20 mg IV). We do not use induction therapy with patients on mechanical circulatory devices or in patients who have received any immunosuppressive therapy within 12 weeks of transplant.

Maintenance immunosuppression generally consists of an antiproflliative drug (azathioprine or mycophenolate), a calcineurin inhibitor (tacrolimus or cyclosporine), and steroids. It is our institutional preference to use mycophenolate because of a reported lower rate of death and treated episodes of rejection when compared to azathioprine (32). Tacrolimus is started postoperatively within 72 hours in patients receiving induction therapy or immediately if serum creatinine is <1.8 mg/dL. Heart recipients without induction therapy receive tacrolimus (1 mg via nasogastric tube) in the operative theater and are converted to sublingual therapy in the rare situation of delayed extubation. We do not use IV tacrolimus because of the difficulty in predicting therapeutic levels and our observation of delayed seizures in patients with transient toxic levels of calcineurin inhibitor. Every attempt is made to wean steroids to 5 mg of prednisone or less within 6 months of transplant, and 30% of heart recipients are steroid free by 2 years (2). We have increasingly used the mammalian target of rapamycin (mTOR) inhibitor rapamycin (Sirolimus) in conjunction with low-dose calcineurin inhibitors to limit calcineurin-induced nephrotoxicity. Rapamycin is not started until 4 to 6 weeks after transplant because of its significant impact on sternal wound healing.
Infection Prophylaxis and Perioperative Risk

Because of the risks of hospitalization and immunosuppression, infection is second only to allograft failure as a cause of early death after cardiac transplantation. Pneumonia is the most common presentation with an historical incidence of approximately 14% to 28% and an overall mortality of 23% to 31% (34). Hospitalization at the time of transplant, postoperative endotracheal intubation for more than 1 day posttransplant, reintubation after transplant, evidence of peritransplant pulmonary infection, use of antilymphocyte induction therapy, and prolonged and excessive use of steroids (>80 mg/day during the first month) are considered significant risk factors (34). It is important to note that nearly 20% of heart transplants occur in patients on mechanical assist devices and that nearly half of all VAD recipients experience infectious complications. These infections rarely involve the device and are not a contraindication to transplant. Registry data suggest that infection requiring IV antibiotics within 2 weeks of transplant is no longer a risk factor for poor operative outcome (2).

The importance of clinical history and serologic screening of potential organ donors cannot be overemphasized given the potential for disease reactivation. Specific characteristics of the donor population vary widely among geographically distinct transplant centers, and ethnic diversity can influence the prevalence of endemic disease. Nearly half of our thoracic organs derive from donors born in areas of endemic Chagas disease (Trypanosoma cruzi), and 20% derive from areas of endemic viral hepatitis B. Geography, not immunosuppression, is also the major risk factor for certain mycoses (e.g., coccidiomycosis, histoplasmosis), and the endemicity of tuberculosis and variola, use of immunization can influence the interpretation of donor serologies. The recent deaths of organ recipients receiving allografts from patients with undiagnosed trypanosomal infection (Trypanosoma cruzi) underscores the increasing globalizaton of the donor population and the need for increasingly sophisticated screening technologies. Our institutional biases for the prophylaxis and treatment of the common bacterial, viral, and fungal pathogens are listed below:

1. Vancomycin (10–15 mg/kg every 12 h) and piperacillin/tazobactam (3.375 gm IV every 6 h) are empiric bacterial prophylaxis. Therapy is stopped at 72 hours after review of donor cultures.

2. Cytomegalovirus seropositivity is not a contraindication for either donor or recipient. Leukocytes are the source of CMV infection, and seronegative blood products should be used in seronegative patients and patients with seronegative allografts. Primary infection, a seropositive (CMV+) organ into a seronegative (CMV−) recipient, is associated with the greatest risk of CMV disease. These patients receive prophylaxis with CMV immune globulin (CytoGam, CMV-IVIG) at 150 mg/kg IV for 7 days followed by valganciclovir (Valcyte) for 1 year (450 mg twice daily [BID] dosed for renal function). Seropositive recipients who receive either CMV-positive or CMV-negative allografts are at moderate to low risk of reactivation disease as are seronegative recipients of CMV-negative transplants. These patients receive prophylactic coverage for 6 months with Valcyte (450 mg orally [PO] BID). Any patient receiving treatment for histologic rejection receives 6 months of prophylactic Valcyte in the context of increased immunosuppression. Active CMV disease is treated with CytoGam (50 to 150 mg/kg IV daily) and a relative withdrawal of immunosuppression to facilitate immunocompetence.

3. Hepatitis B surface antigen seropositivity in potential recipients has been associated with hepatic inflammation or cirrhosis in 37% of heart recipients and is a relative contraindication to transplantation (35). Currently, all patients receive Hep B vaccine prior to transplant (HbsAg positive, HbsAb IgM positive, HbsAb negative). We routinely use HbcAb-positive donor hearts in the context of HbsAg seronegativity as we consider this a sign of prior exposure and not active disease.

4. All patients receive trimethoprim/sulfamethoxazole (Spectra) for Pneumocystis carinii prophylaxis. Fluconazole (100 mg PO every week) is given for mucocutaneous candidiasis prophylaxis as long as patients are receiving steroids, and patients with evidence of fungal colonization (e.g., Aspergillus spp.) are maintained on voriconazole.

In the absence of allograft dysfunction, the decision to treat moderate histologic (2R) rejection with pulse steroids deserves discussion. There is no compelling data that treatment of mild to moderate rejection significantly influences allograft survival, and there is significant evidence that increased steroids and antilymphocyte therapy increase the incidence of infection. Given the variability of histologic interpretation and the inherent possibility of nonrepresentative biopsy tissue, the decision to treat histologic rejection should be approached with caution as this represents the most significant variable in transplant infections.

CLINICAL PEARLS IN CARDIAC TRANSPLANTATION

1. Neurohormonal markers and the circulatory–renal limit predict the need for transplantation, not isolated hemodynamics.

2. Elevated pulmonary vascular resistance, renal insufficiency, and diabetes mellitus are only relative contraindications to transplant.

3. The degree of fixed pulmonary vascular resistance cannot be assessed without unloading the left ventricle.
4. Elevated postoperative PVR exacerbates RV dysfunction.
5. The relationship between histologic rejection and patient outcome remains obscure; microscopic rejection is rarely manifested as graft dysfunction.
6. Balanced risk is the goal of immunosuppression.

References
