Surgical Treatments for Advanced Heart Failure

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In the United States one in eight deaths are due to heart failure or its sequelae, and the prevalence of this disease exceeds 5 million people. Patients with heart failure represent a significantly ill cohort, approximately 80% of men and 70% of women under the age of 65 with heart failure will die within 8 years; one in five will die within 1 year. During the last 20 years, hospital admissions for this disease have increased almost threefold (Fig. 1). Moreover, in 2008, the management of heart failure exceeded $34 billion in direct and indirect costs. Although medical management with diuretics, β-blockers, angiotensin-converting enzyme inhibitors, and other afterload reduction agents has provided symptomatic relief and survival benefit, the survival of the most advanced heart failure patients is dismal with medical management alone. This cohort of advanced heart failure patients benefits from several surgical treatments. Historically, the first successful surgical therapy for end-stage cardiomyopathy was cardiac allograft transplantation. Soon thereafter, the first reports of mechanical cardiac support and replacement were issued. Although several techniques for surgical ventricular restoration (SVR) in the setting of left ventricular (LV) aneurysms have been described over the years, the broader application of these techniques to patients with ischemic cardiomyopathy has occurred during the last decade. This review focuses on LV aneurysm (LVA) repair and SVR, ventricular assist devices (VADs), and cardiac allograft transplantation for the treatment of advanced heart failure. Indications for these procedures are addressed, as well as intraoperative technical features and postoperative management strategies.

SVR

In 1996, working in South America, Dr Randas J. V. Batista first described partial left ventriculectomy with linear reapproximation to restore ventricular function in patients with dilated cardiomyopathy secondary to Chagas Disease. Efforts in this country extended his procedure to individuals with idiopathic dilated cardiomyopathy. In this country extended his procedure to individuals with idiopathic dilated cardiomyopathy.
Unfortunately, approximately 45% of his patients were deceased within the first 2 years. Before Dr Batista’s report on partial left ventriculectomy, in the early 1980s, Dr Vincent Dor developed the endoventricular circular patch plasty for repair of LVAs. A decade later, after observation of the effects of this procedure on LV remodeling, he advocated its usefulness in the treatment of advanced ischemic cardiomyopathy. Although the Batista operation is no longer implemented in the treatment of dilated cardiomyopathy, the Dor procedure has gained popularity due to the promising results of the RESTORE trial and is an integral component of the recently reported Surgical Treatment for Ischemic Heart Failure (STICH) trial.

Ventricular restoration with surgery is built on the observation that the left ventricle undergoes negative remodeling after infarction. This remodeling occurs in the setting of no revascularization and (to a lesser extent) in the setting of appropriate and timely revascularization. After transmural infarction, the diseased area may undergo 3 transformations: (1) necrosis; (2) fibrosis; (3) calcification and often mural thrombosis. Although the infarcted area of the ventricle undergoes these changes, the surrounding “normal tissue” also remodels. Immediately post infarct, the surrounding myocardium is normal. During subsequent months, the remaining myocardium first hypertrophies in compensation for the akinetic/dyskinetic infarcted zone, and then dilates because of increased volumes and wall tension (based on Starling’s and Laplace’s laws respectively). Increased wall tension may trigger myocyte apoptosis in the remote myocardium, resulting grossly in wall thinning and dilation.

Because the viable myocardium is in essence normal and is “remodeled” in response to the changes that occur within the infarcted zone, it logically follows that “restoration” of normal ventricular anatomy should halt further deleterious “remodeling” of normal myocardium. This concept is the fundamental basis for LV reconstruction by endoventricular circular patch plasty. The main goals of this therapy are: (1) removal of the abnormal ventricular wall (the scar); (2) normalization of myocardial fiber alignment; (3) decrease in ventricular wall tension; and (4) restoration of a normal ventricular anatomy (reduce LV volume and restore a more ellipsoid shape).

Fig. 1. Hospital discharges for heart failure (by sex) from 1979 through 2005, including patients characterized as “alive”, “dead”, or “status unknown” at time of discharge. (Data from The Centers for Disease Control National Center for Health Statistics; and the National Heart Lung and Blood Institute. Circulation 2008;117:e25; with permission.)
**Patient Selection**

SVR is most commonly applied in patients with the following features: (1) anteroseptal myocardial infarction secondary to left anterior descending (LAD) occlusion, resulting in a dilated left ventricle (end-diastolic volume index > 100 mL/m²); (2) decreased LV function; (3) focal antero-apical and septal wall motion abnormalities (dyskinesis or akinesis); (4) symptomatic heart failure. Patients who have focal LV antero-apical and septal dysfunction with preservation of function in basal segments may benefit the most from SVR. Furthermore, preserved right ventricular (RV) function is favorable; severe RV dysfunction and pulmonary hypertension have been defined as factors associated with increased procedural risk. Patients in whom SVR is being considered should undergo echocardiography, right- and left-heart catheterization, and cardiac magnetic resonance with late gadolinium enhancement. The goal of these examinations is to assess the viability profile of the LV myocardium, define the extent of scar, as well as to determine areas suitable for revascularization.

**Procedure**

Surgical revascularization of any remaining ischemic areas is typically combined with SVR. Furthermore most surgeons advocate revascularization of the LAD with the internal mammary artery (IMA). Although many of these patients have apical regions of transmural scar, viable regions of septal myocardium invariably remain and benefit from LAD revascularization. Although mild mitral insufficiency may resolve with SVR, moderate and severe mitral insufficiency is also typically addressed surgically. Usually, mitral valve replacement is not necessary and ischemic mitral regurgitation can be addressed with complete ring annuloplasty. Therefore, the SVR procedure is typically performed with concomitant coronary artery bypass graft (CABG) revascularization in patients with ischemic cardiomyopathy. The first step of the procedure consists of conduit harvesting (IMA, SVG, and so forth). Next, cardiopulmonary bypass (CPB) is established, typically using ascending aortic and right atrial canulae. Bicaval venous canulation is employed for those cases that require concomitant mitral valve procedures. Most surgeons also use an LV vent introduced by way of the right superior pulmonary vein. The vent enables better visualization of the inside of the LV and facilitates the deairing process. Aortic cross-clamping and cardioplegic arrest with antegrade and retrograde cardioplegia are typically used to perform the distal coronary anastomoses. After the distal anastomoses are completed, the SVR procedure is undertaken. Some surgeons advocate continued cardioplegic arrest, whereas others have described benefits to performing the SVR after release of the aortic cross-clamp with the heart reperfused. Important steps of the SVR include:

1) The LV is opened through the center of the apical scar, intraventricular thrombus is carefully removed.
2) Endocardium is carefully inspected and palpated to define the border between normal myocardium and scar.
3) At the border of the endocardial scar and normal myocardium, an endoventricular purse string suture is placed (known as the Fontan stitch). Typically a 2-0 polypropylene suture is used; some surgeons prefer to place a double purse string (Figs. 2 and 3B). Usually, the purse string is at least 1 cm distal to the papillary muscle insertions. Placing the purse string too close to the base may result in an LV with inadequate volume. The authors advocate placing this stitch just within the scar tissue, giving the purse string greater strength and avoiding undersizing the ventricular volume.
4) A rubber balloon can be inserted through the purse string and inflated to the theoretical “normal” end-diastolic volume of the patient’s left ventricle (50–60 mL/m² body surface area [BSA]). The Fontan stitch(es) is (are) tied, restoring “normal” ventricular size. The balloon is then deflated and removed (see Fig. 2 inset and see Fig. 3C). Alternatively, some investigators forego “balloon sizing” and base the new ventricle size on preoperative imaging and intraoperative judgment.41

5) Based on the remaining orifice, an endoventricular patch (of either synthetic or autologous material) is fashioned and secured over the orifice (see Fig. 3D). The authors use a Hemashield patch (Boston Scientific, Natick, Massachusetts, USA) secured with a running 2-0 polypropylene suture.

6) The excluded areas of the ventricle can be partially resected and sutured over the patch for further hemostasis.

The procedure continues with placement of the proximal anastamoses of the coronary grafts, usually accomplished with a partial aortic occlusion clamp. The heart is deaired, atrial and ventricular temporary pacing wires are placed, and the patient is carefully weaned from CPB.

Postoperative Management

The initial postoperative management for SVR is similar to other cardiac procedures, with a focus on hemostasis and resolution of coagulopathy and bleeding. Patients who undergo SVR generally have significantly reduced LV function, and postoperative hemodynamic stabilization is another critical goal. Almost all patients are supported...
with intravenous inotropes, usually low-dose epinephrine or intraaortic balloon counterpulsation therapy. Fortunately, this support is typically weaned off within the first 24 to 48 hours.

Another important perioperative problem is the management of ventricular arrhythmias. Ventricular resection may result in greater postoperative myocardial irritability. Avoidance of hypokalemia, hypomagnesemia, early discontinuation of β-adrenergic agonists, and use of β-blockers seems to help reduce arrhythmias. Some patients may require amiodarone or lidocaine infusions. Almost all patients should be evaluated for automated internal cardiac defibrillators.

**Outcomes**

The usefulness of SVR has recently been examined by the STICH trial.26,27 One thousand patients with LV ejection fraction less than 35% were enrolled in the STICH trial and were randomized to receive either CABG alone or CABG with concomitant

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**Fig. 3.** (A) Postmyocardial infarction ventricular remodeling. (B) Through a ventriculotomy made within the myocardial scar region, a purse-string suture is placed along the border of normal myocardium and scar. (C) A ventriculoplasty balloon may be used to ensure proper sizing of the ventricular reconstruction. (D) An endoventricular patch is used to close the remaining defect in the apex of the left ventricle, the scar tissue can be closed over this patch to improve hemostasis. *(From Dor V, Civaia F, Alexandrescu C, et al. The post-myocardial infarction scarred ventricle and congestive heart failure: the preeminence of magnetic resonance imaging for preoperative, intraoperative, and postoperative assessment. J Thorac Cardiovasc Surg 2008;136(6):1405–12; with permission.)*

*S= Septum  L= Lateral wall*
SVR. The follow-up for this portion of the study was at 48 months with the primary end points of death (all causes) and cardiac rehospitalization. Surprisingly, both groups (CABG alone and CABG + SVR) experienced a relative low procedural mortality (<5%) and both groups demonstrated improvement in their heart failure symptoms. There was no difference between the two groups with regards to the primary end points of death and cardiac rehospitalization. These results will probably limit the application of the SVR procedure to patients with dyskinetic or aneurismal segments of LV. The second part of the STICH trial will evaluate the benefits of CABG revascularization relative to medical therapy alone as a treatment of heart failure in patients with ischemic cardiomyopathy.

DESTINATION THERAPY LVAD

Overview of Mechanical Circulatory Support

A variety of mechanical devices have been used to support the circulation and replace ventricular function in the setting of heart failure. Most commonly these devices are mechanical pumps, which achieve complete ventricular unloading and replacement; these devices are termed VADs. The first VAD designs were extracorporeal and connected to the heart by way of canulae and blood tubing. Most commonly, VAD support is used to replace LV function (LVAD), but isolated RV support is possible, as well as biventricular support. Early designs used pneumatic actuation but during the last 2 decades electrically powered designs have become more common. Electrical powering enabled more compact designs in which the entire pump can be implanted in the body, usually inferior to the heart in the abdomen or in a preperitoneal pocket. Fig. 4 illustrates a typical implanted LVAD with drainage of the LV by way of an apical cannula. Blood is then pumped out of the device into a graft attached to the ascending aorta. The pump is electrically driven and a driveline (power cord) exits the patient’s right upper abdominal wall, attaching to small, portable, external batteries enabling untethered activity.

Application of LVADs can be broadly categorized into three groups. First, patients for whom recovery of ventricular function is anticipated and the VAD is used to bridge the patient to recovery. Typically, the duration of support for the recovery strategy is days or weeks. Perhaps the most impressive cases of bridge-to-recovery are patients with acute viral myocarditis. This condition is believed to result from viral myocardial infection and secondary inflammation resulting in profound ventricular dysfunction. Small case series have described patients with viral myocarditis progressing to cardiogenic shock requiring VAD support. In a large percentage of these cases inflammation subsides and ventricular functional recovery occurs, enabling device explantation. Duration of VAD support for viral myocarditis ranges from days to weeks. Other acute conditions, in which ventricular functional recovery may occur during VAD support, include myocardial infarction associated with cardiogenic shock, and profound ventricular dysfunction following heart surgery (postcardiotomy failure). Importantly, for all three of these conditions, a certain subset of patients will not experience recovery and will require long-term support and possibly transplantation.

The second and perhaps most traditional application of LVAD support is for bridging patients with either acute or chronic heart failure, until cardiac transplantation can be performed. These patients are considered to have irreversible ventricular failure and are evaluated and deemed suitable for cardiac transplantation. Before considering LVAD support, patients generally are supported with less invasive therapies such as continuous intravenous inotropes. Implantable LVADs have been used to bridge...
patients to transplant since the late 1980s. Positive outcomes with this application have been important in expanding the field of mechanical circulatory support. Functional recovery, as well as improvement in end-organ function, while on VAD support has been impressive and has served to better prepare candidates for heart transplantation relative to bridging with continuous intravenous inotropes. Transition from the initial, pneumatically driven, implantable LVADs to electrically powered devices led to reduction in the external components for the VAD system, and improved mobility. This advancement enabled patients to be discharged from the hospital while awaiting cardiac transplantation. Discharged patients enjoyed an improved quality of life and in some cases demonstrated an ability to return to employment. Typical waiting periods for cardiac transplantation on VAD support varies due to patient size, blood type and presence of anti-HLA antibodies, but typically ranges from 3 to 6 months. For this duration of support, device malfunction is uncommon and often remedied by replacement of external components. Infection rates ranged from 5% to 10% with the driveline exit site being the most common site of infection. Finally, thromboembolic complications that historically have comprised an important limiting factor for
mechanical circulatory support in general have been acceptable, particularly with devices featuring a textured, blood contacting surface.54

These favorable outcomes using implantable LVADs to bridge patients to transplant have led to several important developments. First, more patients are being bridged to heart transplant with LVADs relative to using continuous intravenous inotropes Fig. 5. The second development seen during the last decade is that patients with end-stage heart failure, who fail to qualify for transplant, are being considered for permanent LVAD support as a substitute for cardiac transplant, so-called destination therapy LVAD (DT LVAD).4 This third application consists of patients who have chronic and severe heart failure that has failed standard medical therapies and who are not candidates for transplant. Thus, permanent LVAD treatment has evolved from the bridge-to-transplant experience as a result of positive and encouraging outcomes. Furthermore, permanent or destination LVAD application is often not entirely distinct from the bridge-to-transplant application because a patient’s eligibility for transplant may change over time. For example, a patient who is felt to be inappropriate for transplant due to obesity may achieve dieting and weight reduction on LVAD support, enabling reconsideration of transplant therapy; the patient may have started as a destination implant but ultimately can be offered transplant.55 Nevertheless, the emergence of destination LVAD therapy for end-stage heart failure has important impact over and above transplant. Cardiac transplant is limited by suitable donors to approximately 2000 patients per year in this country.56 Unfortunately, there are an estimated 100,000 end-stage heart failure patients; therefore, destination LVAD may address a much larger group for whom there are essentially no other therapeutic options.1

**Indications for DT LVAD**

In 2003, as a result of the REMATCH trial, the Food and Drug Administration (FDA) approved the HeartMate XVE (Thoratec Corporation, Pleasanton, California, USA) implantable LVAD for DT.4 Importantly, federal and private insurers have acknowledged the survival and quality-of-life benefits and have agreed to provide reimbursement for this product as DT. Nevertheless, the complexity and cost of the therapy is great and, therefore, indications for treatment are strictly defined. Importantly, the therapy is currently indicated for chronic heart failure; acute heart failure such as post-infarction or acute viral myocarditis is not an indication. Another important mandate is

![Duke Heart Transplants Bridged with VAD](image)

**Fig. 5.** During the past 13 years, use of LVAD systems as bridge to transplantation has increased more than sixfold at our institution.
that patients must have received and essentially failed conventional therapies including medical and potential surgical options. Standard medical therapies included β-blockers, angiotensin-converting enzyme inhibitors, and diuretics. These therapies have all been demonstrated to enhance survival in heart failure patients; FDA guidelines for DT LVAD require that these drugs have been trialed for at least 60 of the last 90 days. As patients progress to end-stage heart failure, they often are unable to tolerate these oral medications owing to the development of a low-output state manifested by hypotension, secondary renal insufficiency, and refractory volume overload including pulmonary edema. At this point, standard oral medications are discontinued and patients are stabilized with intravenous inotropic infusions such as dobutamine (β-adrenergic receptor agonist) or milrinone (phosphodiesterase inhibitor). These inotropic drugs clearly may provide transient symptomatic improvement but they have not been shown to improve survival in any cohort of heart failure patients. Therefore, although failure of oral medical therapy is required before consideration of DT LVAD, prolonged continuous inotropic infusions before referral should be avoided. In addition, other conventional surgical therapies should be considered, if appropriate, before DT LVAD. For example, some patients with ischemic cardiomyopathy may benefit from revascularization. Other patients with end-stage heart failure may have important aortic or mitral valvular dysfunction that can be addressed with surgery. If there is significant hope for recovery of functional capacity, and the procedural risk is acceptable, then these conventional surgical options should be attempted.

Another important treatment option for end-stage heart failure is biventricular pacing for ventricular resynchronization. In select patients with prolonged QRS duration, this pacing therapy has been shown to improve symptoms and functional class. Therefore, given the relative noninvasive nature of this option, patients with the appropriate indications should first undergo a trial of biventricular pacing. Practically, most patients who are referred for DT LVAD have failed biventricular pacing.

TRANSPLANT INELIGIBILITY

An additional important requirement for DT LVAD consideration is that patients be evaluated and found ineligible for transplant. When a medical center offering DT LVAD therapy does not offer cardiac transplant evaluation, a special relationship with a transplant center needs to be established so that patients can be evaluated for transplant before being considered for permanent, implantable LVAD. Perhaps the most common reason why DT LVAD patients are considered ineligible for transplant is advanced age. Typically, many transplant centers have established age 65 or 70 to be the upper limit. This limit is consistent with International Society of Heart & Lung Transplantation (ISHLT) registry data, which demonstrate reduced outcomes with transplant in this older subset. Other common reasons for transplant ineligibility include obesity or increased body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters). Importantly, these patients may achieve weight reduction during LVAD support and be reconsidered for transplant. Other reasons for transplant ineligibility include extremely high levels for anti-HLA antibodies, which preclude adequate donor matching. Also history of recent malignancy and severe heart failure is an important factor that makes patients ineligible for transplant due to risks of reactivation of malignancy with immunosuppression. An example is the patient who receives adriamycin chemotherapy and suffers secondary cardiac toxicity. Furthermore, other end-organ dysfunction, such as some degree of primary
pulmonary disease or renal insufficiency, may make heart failure patients ineligible for transplant but still suitable for LVAD consideration. In addition, severe pulmonary hypertension or increased pulmonary vascular resistance may disqualify patients from consideration of transplant, but they may still be suitable for DT LVAD.

Importantly, common to the evaluation for transplant and DT LVAD, is the psychological and social screening. Included in this assessment is an evaluation for medical compliance. Patients who are found to be psychologically unstable are not eligible for either therapy. Similarly, lack of social support or demonstration of active substance abuse makes a patient ineligible for either therapy. In summary, the needs for social support, psychological stability, and medical compliance are similar for transplant and LVAD therapy.

**Determination of Severity of Heart Failure**

Given the procedural risks of LVAD therapy, it is important that stable heart failure patients with life expectancy greater than 1 or 2 years not be offered this therapy. On the other hand, patients who have progressed to secondary end-organ dysfunction may have missed the optimal treatment window, as studies have shown markedly increased procedural risk. Therefore, proper timing is critical; unfortunately, predicting survival is challenging for advanced heart failure. Workup should include exercise testing whenever possible; the maximal oxygen consumption less than 14 mL/kg/min has been associated with high 1-year mortality and should serve as an indication of heart failure severity warranting DT LVAD. Other markers for high heart failure mortality include repeated hospitalizations for decompensation, cardiorenal syndrome, and clinical need for continuous inotropic infusions. Poor hemodynamics also predict negative outcomes and should be obtained routinely by right-heart catheterization. Evaluation and intervention before secondary end-organ dysfunction, malnutrition, or complicating infection is critical to successful outcomes and requires a multidisciplinary advanced heart failure team.

**Preoperative Assessment and Optimization**

There is a trend toward more elective implants for DT LVADs. This strategy has emerged from the observation that so-called crash-and-burn patients have high procedural mortality, which is probably unacceptable given the cost and complexity of this treatment. Thus, hemodynamic optimization and improvement of end-organ function is an important focus before taking the patient to the operating room. Patients who are unstable may be optimized with intravenous inotropes and invasive monitoring. Those who fail these measures may benefit from temporary mechanical support before the implantable LVAD. Usually, this consists of intraaortic balloon pump to improve hemodynamics. Although typically employed for ischemic heart conditions, our experience suggests patients with advanced myopathies of any cause derive benefit from periods of intraaortic balloon pump (IABP) support. Other types of temporary support include percutaneous LVADs such as the Tandem Heart (Cardiac Assist, Inc., Pittsburgh, Pennsylvania, USA) or the Impella (AbioMed, Inc., Danvers, Massachusetts, USA) devices. These devices are capable of LV unloading and achieve flows up to 4 L/min. With these temporary devices, many patients will show evidence for improvement in end-organ perfusion such as resolution of oliguria, improvement in serum creatinine and normalization of serum hepatocellular enzyme levels. Patients who fail to respond to these temporary support measures are probably at high procedural risks for the implantable LVAD.

Another important element of the preoperative evaluation is to rule out, and treat any signs of, infection. In general, any fever in the preoperative period warrants
pan-culturing and in some instances empiric antibiotics. This aggressive course is indicated because infection is an important cause of heart failure, decompensation, and death. In addition, infection represents a common morbidity and cause of death post-LVAD implant. In general, old lines should be replaced before the implant procedure. Preprocedural prophylactic antibiotics should include vancomycin, as well as an agent effective for gram-negative organisms and an antifungal agent. All 3 should be administered before the skin incision.

**Intraoperative Procedure**

Intraoperative transesophageal echocardiogram is performed after initiation of anesthesia. It is important to exclude the presence of a patent foramen ovale or any other septal defect. With LV unloading, such defects can allow significant right-to-left shunting and systemic desaturation. Any identified defect should be repaired. Competency of the aortic valve is also evaluated: significant aortic insufficiency (AI) leads to regurgitant volume and reduced systemic output. Severe AI warrants replacement or repair (although need for this additional intervention substantially increases the risk of the procedure). Severe tricuspid insufficiency is often surgically addressed and probably does not add significant additional risk. Most surgeons agree that mitral insufficiency does not need to be corrected because the LV becomes unloaded after LVAD placement.

Most implantable LVADs are placed by way of a median sternotomy, which affords good exposure of the ascending aorta for outflow graft attachment and of the LV apex, which is typically canulated for inflow to the pump. Typically, the incision is extended downward onto the upper abdomen, enabling placement of the pump just inferior to the heart in either a preperitoneal pocket or directly into the abdominal cavity. As LVAD pump designs have become smaller, extension of the median sternotomy may not be necessary. The dissection of the pump pocket should be performed first, before heparin administration; the driveline is usually tunneled out of the right upper abdomen, again before heparin administration.

The next step of the procedure typically involves attachment of the pump to the native heart. There are two sites of attachment that consist of the apical LV cannula and the outflow graft to the ascending aorta. The order in which these steps are performed is not critical and some surgeons prefer one attachment before the other. Furthermore, although CPB is typically employed for these attachments, the placement of the apical canula and the outflow graft can be performed without CPB. CPB provides an element of safety and control, but proponents of reducing the use of CPB argue that bleeding and coagulopathy are reduced when CPB is avoided.

The apical canula is placed after removal of a core of LV apical myocardium. Usually, a series of felt-pledget reinforced 2-0 sutures are used to secure a synthetic ring to which the apical canula is attached. Care is taken to resect any trabeculations in the LV apex that might interfere with drainage of the LV into the canula. Similarly, any LV thrombus, which commonly develops with end-stage heart failure, must be removed. Typically, the apical left anterior descending coronary artery is preserved. Furthermore, care is taken to direct the apical canula away from the septum toward the mitral valve orifice. Occasionally, particularly in smaller LVs, the apical canula can become pushed into the heart, leading to obstruction of drainage by either the septum or the lateral free wall. The remedy consists of repositioning the canula and retracting it away from the ventricular apex. The attachment of the outflow graft consists of an end-to-side anastomosis to the ascending aorta; typically this is accomplished with a running 4-0 propylene suture. Many cases may be reoperative with the patient having had prior coronary bypass grafts; in these instances care must be taken
to avoid injury to these grafts that may result in regions of myocardial ischemia, ischemic ventricular arrhythmias, and, in some cases, RV dysfunction.

Following placement of the canulae, the next steps consist of deairing, pump activation, and weaning from CPB. Typically, these procedures should be performed in a field flooded with CO₂, thus reducing the negative impact of embolized air. In addition to conventional deairing strategies, submerging the pump in warm saline may be helpful. Initially, pump settings should be reduced to avoid complete emptying of the LV and creation of suction that could also lead to entrainment of air. Optimizing RV function also helps keep the LV filled and prevents entrainment of air. After the patient is safely weaned off bypass, the heparin is reversed and clots will form in the field and around the outside of the pump. After the protamine reversal, the risk of air entrainment is reduced and the pump speed can be more safely increased. An unfortunate scenario occurs when air is present and enters the aorta, leading to obstruction in the right coronary artery. If the air persists in the right coronary artery, RV ischemia and dysfunction will occur. This occurrence in turn results in underfilling of the LV, potential suction with further entrainment of air; thus, a negative cycle can lead to circulatory failure and the need to return to CPB. Attention to details and focus on maintaining good RV performance and avoiding air entrainment at the time the patient is weaned off CPB helps avoid this negative scenario.

Therefore, in initiating LVAD support, an important concern is RV performance. In general, LV unloading should reduce the afterload of the RV and improve RV output. Nevertheless, RV dysfunction is common after implantable LVAD procedures. Adequate heart rate and an atrioventricular synchronous rhythm help to optimize RV performance. Inotropic support is typically employed in the form of low-dose epinephrine or dobutamine. Excessive leftward septal shift can occur if pump speed is too high; this should be avoided as it can lead to reduced RV function as well as worsening tricuspid insufficiency. Additional agents should be employed to reduce pulmonary vascular resistance; for example, inhaled nitric oxide has been shown to reduce pulmonary vascular resistance and increase LVAD output. This agent is particularly useful because it does not have systemic effect. Iloprost (inhaled prostaglandin) has been similarly used and seems to have little systemic effect. If these traditional strategies do not achieve adequate right-heart performance, a final option is mechanical support in the form of an RVAD. Usually, RVAD placement requires canulation of the right atrium and pulmonary artery. Temporary RVAD support is often all that is required and devices such as the CentriMag have been used at our institution.

Postoperative Care

Immediately after implant, bleeding is an important concern: many patients will have hepatic insufficiency and coagulopathy. In addition, temporary mechanical support, such as IABP before the LVAD, may have resulted in platelet dysfunction. Furthermore, recent studies have shown that LVAD support may affect von Willebrand factor and induce a form of acquired von Willebrand disease. For all these reasons, an important initial focus is achieving normal platelet function.

RV performance remains an important issue in the early postoperative period. Some investigators have shown that many patients supported with implantable LVADs will have ongoing intravenous inotropic requirements for RV dysfunction. Most of these patients will ultimately be weaned off inotropes and achieve normal hemodynamics, but support for 2 to 3 weeks is not uncommon in a small fraction of patients. Furthermore, ongoing support with diuretics is not uncommon for peripheral edema. For patients with axial flow or centrifugal pumps, reassessment of pump speed should be performed to ensure complete LV unloading, which translates into reduced
afterload for the RV. Ongoing attention to adequate heart rate and rhythm, and avoidance of arrhythmias, are also important to optimize RV performance. Pulmonary processes such as major effusions or atelectasis may have a negative impact on pulmonary vascular resistance leading to reduced RV output and elevated central venous pressures, therefore these pulmonary conditions should also be corrected.

**Outcomes**

The REMATCH study was a prospective randomized trial that compared optimal medical management to implantable LVAD in patients with end-stage heart disease, who were ineligible for cardiac transplantation. Most patients who were randomized to these two therapies were of ages greater than 65, dependent on continuous intravenous inotropes, and had evidence of secondary renal insufficiency. The only device used in this trial was the vented electric HeartMate XVE. This device is a larger first-generation pump that provides pulsatile flow. The trial demonstrated improved survival and quality of life with the LVAD treatment relative to optimal medical management (Fig. 6). Unfortunately, mortality and morbidity remained high even in the LVAD treatment arm. Thus the trial supported permanent use of implantable LVADs for patients who are transplant ineligible, but also highlighted many of the limitations of the HeartMate XVE design.

The REMATCH trial led to FDA approval of the HeartMate XVE as a DT. Specific criteria for DT LVAD therapy have been defined by the FDA, and a postapproval registry was mandated to further evaluate outcomes. Furthermore, DT LVAD therapy was limited to designated hospitals, as controlled by the Joint Commission for Hospital Accreditation. The therapy has been slow to develop with the HeartMate XVE, but outcomes have generally improved post-REMATCH (Fig. 7).

Despite improving outcomes, the broader application of the HeartMate XVE device was limited by the substantial morbidity as outlined in the REMATCH trial. The morbidity was in part due to the large size of the device, which prevented implantation.

![Fig. 6. Kaplan-Meier survival estimates from the REMATCH trial. Patients supported by the HeartMate XVE LVAD had significantly better survival compared with those on maximal medical therapy (P = .001). (From Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001;345(20):1435–43; with permission.)](image-url)
in most female patients. The larger size required an extended incision, which probably also impacted postoperative recovery. Related to the increased size was a substantial risk for infection. Device-related infections included driveline infections, infection of the pump pocket, and other infections involving blood-contacting elements of the device (so-called LVAD endocarditis). These different infections were difficult to treat and eradicate, and proved limiting. The most important limitation for this LVAD design, however, was durability. The HeartMate XVE seemed durable when used for several months as a bridge to transplant, but more prolonged use as a destination device revealed definite durability issues. The device predictably failed between 1 and 2 years. Sites of failure included the bearings and the inflow valve. Although device replacement has been performed successfully, it represented another major procedure including the need for CPB support. Thus, as newer devices evolved, the most important goal was improved durability.

NEWER IMPLANTABLE LVAD DESIGNS

First-generation, implantable LVADs featured pulsatile delivery of blood to the systemic circulation with stroke volumes similar to those of the native heart. Newer-generation devices have progressed to continuous-flow designs. This design change offered several important theoretical advantages: first, in general, continuous-flow pumps could be electromagnetically driven, with fewer bearings and without valves; thus, theoretically they would have greater durability. Second, continuous-flow pumps lacked a diastolic phase during which blood would be stagnant within the device; this feature theoretically should reduce thromboembolic risk. Finally, because these devices do not have to accommodate the human stroke volume, the size is considerably reduced relative to pulsatile pumps. Potential limitations for continuous-flow devices also existed, including potential for greater blood agitation and hemolysis, particularly at higher pump revolutions per minute. Also, the lack of pulsatility may result in inadequate perfusion of certain end-organ beds. Fortunately, early clinical

Fig. 7. Current-era DT LVAD at LDS Hospital in Salt Lake City, Utah, (LDSH DT) demonstrates significantly improved 2-year survival compared with the original REMATCH trial patients who received LVAD therapy (LVAD REMATCH) \( P < .0001 \). (From Long JW, AH Healy, Rasmussen BY, et al. Improving outcomes with long-term "destination" therapy using left ventricular assist devices. J Thorac Cardiovasc Surg 2008;135(6):1353–61; with permission.)
results with continuous-flow devices seem to support these theoretical advantages and have disproven some of the potential limitations. Two continuous-flow designs that have been clinically investigated are axial-flow and centrifugal pumps.


![Figure 8. Second-generation LVAD devices. (Top left) The Debakey Heart Assist 5 by Micromed Cardiovascular, Houston, Texas, USA. (Bottom left) The Jarvik 2000 by Jarvik Heart, New York, USA. (Right) The HeartMate II by Thoratec Corporation, Pleasanton, California, USA.](image1)


HeartMate II BTT Clinical Trial Hemodynamic Improvement

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![Figure 9. The HeartMate II bridge-to-transplant trial demonstrated an improvement in the hemodynamic profile of patients who received the device within 1 day of implant. Cardiac index improved by an average of more than 0.7 L/min/BSA (left) and pulmonary capillary wedge pressure (PCWP) decreased by more than 6 mmHg (right). (Data from John R, Kamdar F, Liao K, et al. Improved survival and decreasing incidence of adverse events with the Heartmate II left ventricular assist device as bridge-to-transplant therapy. Ann Thorac Surg 2008;86:1227.)](image2)

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include the HeartMate II (Thoratec Corporation, Pleasanton, California, USA), DeBakey HeartAssist 5 (Micromed Cardiovascular, Inc., Houston, Texas, USA) and the Jarvik 2000 (Jarvik Heart, Inc, New York, USA) (Fig. 8). The greatest clinical experience has been with the HeartMate II pump. This device was trialed in two phases: the first was with the pump used as a bridge to transplant. In this bridge study, outcomes with the HeartMate II were compared with historical performance measures obtained with the HeartMate XVE device. The HeartMate II bridge-to-transplant trial showed the device to be capable of restoring normal hemodynamics (Fig. 9). In addition, functional recovery with the HeartMate II was impressive, with most patients returning to New York Heart Association (NYHA) class I or II (Fig. 10). Furthermore, morbidity with the HeartMate II appeared reduced relative to historical outcomes with the HeartMate XVE. Based on these results, the HeartMate II device has been approved for the bridge-to-transplant indication.\(^7^4\)

The second phase of investigation has examined the HeartMate II as DT. The DT trial randomized patients to either the HeartMate II or HeartMate XVE. This trial also included a small cohort who were not randomized because they were ineligible for the HeartMate XVE because of low BSA. Another group consisted of patients who required device replacement, and these again were not randomized. The single most important observation from this study was the improved durability of the HeartMate II relative to HeartMate XVE. There were few reports of HeartMate II pump failure or wear-out; the most common serious device failure related to driveline malfunctions that were generally caused by trauma. These driveline failures occasionally required device replacement, although many of the leads could be repaired.\(^7^5\) The device durability seems to be greater than 3 or 4 years.

The thromboembolic profile for the HeartMate II device also seems to be favorable, and equivalent to that of the HeartMate XVE.\(^7^6\) Although initial anticoagulation guidelines included coumadin, aspirin, and dipyridimole, bleeding complications appeared to be the more frequent and concerning adverse event. Patients appeared to have increased incidence of gastrointestinal bleeds; these observations led to progressive reduction in target international normalized ratio (INR) levels as well as reduced use of antiplatelet agents. Other investigators have shown reduced von Willebrand factor function, which may be related to loss of high–molecular-weight multimers that are

![HeartMate II BTT Clinical Trial Functional Improvement](image)

**Fig. 10.** The HeartMate II bridge-to-transplant trial also demonstrated an improvement in the functional status of patients who received the device. Six-minute walking distance (left) and the proportion of patients with NYHA class I or II heart failure (right) increased steadily during the course of LVAD therapy. (Data from John R, Kamdar F, Liao K, et al. Improved survival and decreasing incidence of adverse events with the Heartmate II left ventricular assist device as bridge-to-transplant therapy. Ann Thorac Surg 2008;86:1227.)
normally responsible for binding to platelets and collagen. It is unclear if this acquired von Willebrand condition is device-specific.

Implantable LVADs with a centrifugal design have also undergone clinical testing. These designs feature an electromagnetically driven rotor that is magnetically levitated. This design therefore lacks bearings and, theoretically, may be the most durable (Fig. 11). Examples of this design are the VentrAssist (Ventracor, Inc, Foster City, California, USA), the Levacor (AbioMed, Inc), and the HeartWare HVAD (Thoratec Corporation, Pleasanton, California, USA), which are similarly undergoing testing for the bridge-to-transplant indication as well as for DT.

DESTINATION LVAD THERAPY, FUTURE FRONTIERS

The balance of thromboembolism and bleeding will always remain an important challenge for mechanical circulatory support. Pump designs and blood contacting materials remain an important focus for LVADs. Textured surfaces seem to show reduced thrombosis risk relative to smooth surfaces. Textured titanium is now commonly employed for blood-contacting elements. Another potentially important area of research involves development of biocompatible surfaces or coatings. For example, some devices have employed heparin coating for blood-contacting surfaces, but this strategy has not proven clinically beneficial. Another experimental strategy involves expansion of endothelial progenitor cells and seeding of LVAD materials to create a monolayer of endothelium lining the inside of the pump. This strategy would require a preprocedure incubation of the pump surfaces with endothelial progenitor cells. Preliminary studies suggest that these cells can become seated and withstand expected shear forces.

Another important limitation for current LVAD systems is infection. Infections may involve the driveline or be more complex, with involvement of the pump pocket or of blood-contacting elements of the device. Infection rates seem much higher for LVADs with drivelines exiting the body relative to other implants in which there is no exiting part. For example, pacemakers or automatic implanted cardiac defibrillators have long-term infection rates of less than 1%; unfortunately, implantable LVADs with exiting drivelines may have long-term major infection rates closer to 10%. Strategies to rectify these higher rates have included attempts at completely implanted

Fig. 11. Third generation LVAD devices, like the VentrAssist by Ventracor, Foster City, California, USA (left), and the HeartWare by Thoratec Corporation, Pleasanton, California, USA (right), have magnetically levitated impellers so there are no points of physical contact and therefore, theoretically, no possibility for wear. (From Aggarwal S, Cheema F, Oz MC, et al. Long-term mechanical circulatory support. Card Surg Adult 2008;3:1609–28; Courtesy of Ventracor, Inc, Foster City, California; with permission. Heartware: http://www.heartware.com.au.)
systems that are driven by transcutaneous energy transmission. Another effort has focused on reducing the size of the driveline.

An important frontier involves efforts to achieve recovery of ventricular function even for chronic heart failure patients supported on LVADs. Theoretically, this might convert permanent LVAD patients into patients who receive device support for months or years until sufficient reverse remodeling is achieved, such that device weaning and removal would be possible. Indeed, multiple basic studies have shown that LVAD mechanical unloading results in positive cellular and molecular changes, which constitute the process of reverse remodeling. The clinical results that are most supportive for this potential strategy are from the Harefield group in England. This group has reported on almost two dozen chronic heart failure patients who underwent treatment with LVAD unloading in combination with standard oral heart failure medications. In addition, patients were treated with the experimental agent clembuterol, which acts as a β-2 adrenergic receptor and has anabolic steroid properties. This group has developed a complex LVAD-weaning protocol. Many of the patients achieved LVAD-explantation with long-term freedom from significant heart failure symptoms. Other investigators have introduced the concept of stem cell or gene therapy modification of the native heart during LVAD support.

In summary, as smaller and more durable LVAD designs have developed, other frontiers of research are focused on improved biocompatibility and developing adjuvant treatment strategies to enable recovery of the native heart. With these ongoing efforts, implantable LVAD therapy should play an expanding role in the future treatment of end-stage heart failure.

CARDIAC ALLOGRAFT TRANSPLANTATION

Cardiac allograft transplantation is indicated in patients with symptomatic end-stage heart failure whose life expectancy is considered to be less than 1 or 2 years. Allocation of donor organs is coordinated by local organ procurement organizations (OPOs) under the oversight of the United Network for Organ Sharing (UNOS). UNOS maintains a prioritized waiting list of all patients in the country who need transplantation. Donated hearts are first allocated to the highest priority (status 1A and 1B) local (within the same OPO) recipients who are size- and ABO blood-group compatible. If no high priority local recipients accept the organ, then the organ is offered regionally to status 1A and 1B patients in a stepwise pattern before it is offered to local and regional status two patients. This allocation scheme was last modified in July of 2006 to redistribute organ allocation to more critically ill recipients (Fig. 12).

Patient Selection

Cardiac transplantation can be offered to patients with end-stage heart failure due to many disease etiologies, the most common of which are coronary artery disease and nonischemic (idiopathic) dilated cardiomyopathy. Other less common causes that require transplantation include congenital conditions, valvular heart disease, and retransplantation. The general distribution of these causes for heart transplantation has not changed significantly during the past 10 to 20 years.

Probably the single most important component impacting survival after cardiac transplantation is recipient selection. This procedure can provide considerable improvements in mortality and quality of life in appropriate patients. To better delineate which patients will benefit the most, there are specific inclusion and exclusion criteria for transplantation. Stable patients who are being considered for cardiac transplantation should undergo cardiopulmonary exercise stress testing. Patients whose
peak VO$_2$ is less than or equal to 14 mL/kg/min off β-blockade or less than or equal to 12 mL/kg/min on β-blockade are felt to have increased 1-year mortality and should be considered as candidates for cardiac transplantation (Fig. 13).$^{80,81}$ Patients with VO$_2$ less than or equal to 10 mL/kg/min seem to benefit the most from cardiac transplantation.$^{80}$ For patients with borderline VO$_2$, the use of a heart failure survival score may help guide the selection of appropriate transplantation candidates. In addition, patients being evaluated for transplantation should undergo right-heart catheterization. Because most donor right ventricles are not accustomed to elevated resistance within the pulmonary vasculature, right-heart failure after cardiac transplantation represents a significant morbidity and mortality. Patients with pulmonary vascular resistance of more than five Wood units or transpulmonary gradient of greater than 20 mm Hg that does not respond to LV unloading (either with a vasodilator or by mechanical means) are at increased risk for mortality after transplantation.$^{80}$ This

![Fig. 12. Allocation changes in July 2006 resulted in an increase in transplants for status 1A and 1B patients compared with status 2 patients. (Data from 2007 annual report of the U.S. organ procurement and transplantation network and the scientific registry of transplant recipients: transplant data 1997–2006. H. S. B. Health Resources and Services Administration, Division of Transplantation. Rockville, Maryland, USA.)](image1)

![Fig. 13. Patients with peak VO$_2$ values of less than 14 mL/kg/min have significantly reduced mortality. These patients would likely benefit most from cardiac transplantation. (Data from Mancini D, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778–86.)](image2)
risk is augmented if, in the setting of one or more of the above risk factors, the pulmonary artery systolic pressure exceeds 60 mm Hg. Another study has suggested that if the patient’s pulmonary vascular resistance can be decreased to less than 2.5 Wood units, but, in doing so, the systemic systolic blood pressure drops to less than 85 mm Hg, then the patient remains at a high risk for early post-transplant right-heart failure and death.80

Aside from hemodynamic considerations, the patient’s comorbidity profile must be considered before listing for transplantation. Ideal candidates have isolated heart failure with preservation of other end-organ function. Other noncardiac end-organ dysfunction and systemic medical conditions often exclude patients from cardiac transplantation. Specific contraindications are listed in Box 1. In addition to these contraindications, special consideration should be made to the patient’s immune response to a panel of reactive antibodies (PRA). Recently, predetermination of anti-HLA antibody specificity has enabled virtual crossmatches between these recipients and prospective donors.82 Still, severely elevated PRA may practically preclude successful transplantation.

Donor Selection

Potential heart donors are declared brain dead by 2 local physicians who are not part of the transplant team. After brain-death declaration, organ-procurement agents interview the potential donor’s family and care-givers to obtain data regarding cause of death, previous medical and surgical history, social history (including any high-risk behaviors), body size, blood type, and viral serologies (including HIV and hepatitis). Additional donor studies are obtained to examine cardiac structure and function; these include ECG, cardiac enzymes, echocardiography, and Swan-Ganz catheterization with hemodynamic measurements. Assessment of intravenous inotropic requirements should also be reviewed. Coronary angiography is obtained selectively in older (age >40 years) or high-risk donors, but this may not be available at all institutions. Donors who are HIV positive, have severe ventricular dysfunction, or severe coronary artery disease

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<td>Primary severe pulmonary insufficiency</td>
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<td>Severely symptomatic cerebrovascular disease that cannot be revascularized</td>
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<td>Peripheral vascular disease that will limit postoperative rehabilitation and is not amenable to revascularization</td>
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should not be used for transplantation. Donors with positive hepatitis serologies, history of cancer, mildly to moderately depressed cardiac function, and noncritical coronary disease may not be ideal for use in standard list transplant patients, but may be used for critically ill recipients or those in alternate list programs (see below). In addition to

Fig. 14. After recipient cardiectomy, there should be sufficient cuffs of SVC, IVC, LA, aorta, and PA to perform the necessary anastomoses without tension. (From Miniati DN, Robbins RC. Heart transplantation: a thirty-year perspective. Annu Rev Med 2002;53(1):189; with permission.)

Fig. 15. The left atrial anastomosis is performed with a single running suture that secures the donor left atrial cuff to the recipient. (From Gamel AE, Yonan NA, Rahman AN, et al. Alternative heart transplantation technique. Ann Thorac Surg 1995;59(1):258–60; with permission.)
consideration of the donor features, the transplant surgeon must match donor-recipient factors such as size, ABO compatibility, and HLA-antibody compatibility as well as logistic factors including ischemic time.83

**Organ Preservation**

Most donor hearts are currently preserved with specialized cold colloid solutions and placed in cold storage at 2–4°C. These colloid solutions are designed to prevent myocardial edema; examples include University of Wisconsin and Celsior solutions. This cold-storage technique yields good results for total ischemic times less than 4 hours. Recently, studies using warm perfused storage have been undertaken with hopes of improving and extending preservation.

**Procedure**

Orthotopic cardiac transplantation is performed through a median sternotomy using total CPB, achieved with bicaval snaring and cross-clamping of the aorta. The recipient cardiectomy is performed leaving sufficient lengths of aorta, pulmonary artery, and right and left atrial cuffs (Fig. 14). Next, the donor heart is removed from its storage solution, inspected, and prepared for implant. The donor left atrial cuff is anastomosed to the recipient’s left atrial cuff using a running 3-0 polypropylene suture (Fig. 15). The right atrium is then anastomosed using either an atrial level (Fig. 16) or a bicaval (Fig. 17) technique. In recent years, there has been increasing use of bicaval anastomoses.84 In the bicaval technique, the inferior and superior vena cavae of the recipient and donors are individually anastomosed. Proponents of the bicaval attachment have argued that, relative to an atrial level anastomosis, this technique preserves sinoatrial (SA) node function, results in less tricuspid insufficiency, and better RV function.

*Fig. 16.* If an atrial-level anastomosis is intended for the right atrium, an appropriate cuff of RA should be left during recipient cardiectomy. The donor right atrium is prepared with ligation of the SVC and opening of the right atrium along an imaginary line connecting the IVC to the tip of the right atrial appendage. (From Schnoor M, Schäfer T, Lühmann D, et al. Bicaval versus standard technique in orthotopic heart transplantation: a systematic review and meta-analysis. J Thorac Cardiovasc Surg 2007;134(5):1322–31; with permission.)
Finally, end-to-end pulmonary artery and aortic anastomoses are created, completing the transplant procedure.

**Postoperative Management**

After heart transplant, patients need to be monitored closely for right-heart dysfunction. In fact, nearly 20% of early postoperative deaths after cardiac transplantation occur due to RV failure. Typically, right-heart dysfunction is managed by providing adequate heart rate and atrioventricular synchrony. Inotropic support with low-dose epinephrine, dobutamine, and milrinone is common. Agents that increase pulmonary vascular constriction should be avoided. For severe right heart failure (decreasing cardiac output in the setting of increasing central venous pressure and decreasing pulmonary artery pressures), inhaled nitric oxide, temporary right VADs, or even extracorporeal membrane oxygenation are used.

**Immune Suppression**

The role of induction therapy for cardiac transplantation is controversial. Although some have argued that induction therapy decreases the incidence of rejection, there are data that show that this decrease in rejection does not improve overall survival. Moreover, advocates of induction therapy tout its safety, but those opposed refer to studies that describe increased risk of infection and malignancy. Many programs use induction therapy as a “renal sparing” strategy that allows for delaying the administration of calcineurin inhibitors postoperatively. Zenapax, thymoglobulin, and simulect, which are monoclonal anti-interleukin-2 receptor antibodies, have been used more frequently for induction therapy in recent years, whereas OKT3 and antithymocyte globulin, which were previously used as induction therapy in the 1990s, have lost considerable popularity.
Regardless of the use of induction therapy, most cardiac transplant patients receive methylprednisilone 1000 mg IV before reperfusion of the heart along with a dose of an antimetabolite. A randomized, double-blind trial comparing azathioprine (AZA) to mycophenolate mofetil (MMF) demonstrated increased survival and decreased graft loss for patients treated with MMF. Therefore, the antimetabolite agent of choice has transitioned from AZA to MMF. A corticosteroid taper is then instituted during the following week and calcineurin inhibitors are started either immediately postoperatively or after a 24- to 48-hour delay (depending on the use of induction therapy). Again, in recent years, the favored calcineurin inhibitor has transitioned from cyclosporine to tacrolimus. Although, historically, most patients were maintained on corticosteroids for many years after the transplant, in recent years there has been increasing use of corticosteroid withdrawal protocols at 1 and 2 years postoperatively. Studies suggest that earlier weaning of steroids in select patients has not resulted in greater rejection. Limiting corticosteroids should reduce a variety of complications, most importantly infections.

Management of immunosuppression is a balance between over-immunosuppression, which can result in infection, malignancy, bone marrow suppression, or other toxicities versus under-immunosuppression, which can lead to rejection. Ideally, patients are kept within the appropriate range, in which they avoid rejection and the complications of over-immunosuppression. This balance has traditionally been achieved by following blood levels of the calcineurin inhibitors and performing endomyocardial biopsy (Fig. 18). Endomyocardial biopsies are performed at routine intervals and with any change in clinical status, providing direct information on immune-cell infiltration in the allograft. Based on these results, patients’ immunosuppression can be appropriately modified.

Unfortunately, endomyocardial biopsy is time-consuming and expensive. Moreover, it can be limited by sampling error and interobserver variability. Finally, because it is an invasive procedure, there is an associated major morbidity of approximately 1%. For these reasons, a noninvasive method for detection of rejection has been an active area of investigation. Recently, the Cardiac Allograft Gene Expression Observational (CARGO) Study developed a microarray gene expression map (the AlloMap) to distinguish between ISHLT grade 0 and grade 3A acute cellular rejection based on mononuclear cell mRNAs in peripheral blood. This methodology examines the gene-expression profiles of peripheral blood mononuclear cells (PBMCs) and generates a score (between 0 and 40) based on the relative expression of a set of 20 genes. Some of these genes gauge the immune response process, whereas others serve to normalize the score. The score has been shown to have a positive predictive value of 6.8% and a negative predictive value of 99.6% for grade 3A rejection (Fig. 19). Many centers use AlloMap testing after the first postoperative year. A low score effectively rules out grade 3A rejection, eliminating the need for invasive biopsy. On the other hand, a high AlloMap score requires a biopsy. After the first postoperative year, the incidence of rejection is low and the AlloMap score helps significantly reduce unnecessary biopsies.

Complications

During the immediate postoperative period and during the first post-transplant year, primary graft failure is an important cause of morbidity and mortality. In this time period, the incidence of profound graft dysfunction necessitating mechanical support is between 5% and 10%. Moreover, during the first post-transplant year, infection and rejection are also important causes of death. After the fifth year, cardiac graft vasculopathy represents the most common cause of death, accounting for
Fig. 18. Surveillance RV endomyocardial biopsy is performed by passing a biotome through the right internal jugular vein using a modified Seldinger method into the apex of the right ventricle. A biopsy is then obtained using fluoroscopic guidance and the specimen is then removed for pathologic analysis. (Reprinted with permission from Netter Anatomy Illustration Collection, © Elsevier Inc. All rights reserved.)

Fig. 19. The distribution of AlloMap scores is predictive of the risk of 3A rejection. If AlloMap score exceeds the cutoff value, confirmatory endomyocardial biopsy is required. (From Fang KC. Clinical utilities of peripheral blood gene expression profiling in the management of cardiac transplant patients. J Immunotoxicol 2007;4(3):209–17; with permission.)
approximately 30% of late deaths. Similarly, after the fifth year, malignancy accounts for approximately 20% of deaths.\textsuperscript{79}

**Outcomes**

Despite the limitations of rejection and infection, cardiac transplantation remains the single most effective therapy for end-stage heart failure. Although mortality is greatest within the first postoperative year (approximately 10%), annual mortality falls to less

![Heart Transplant Survival by ERA](image)

**Fig. 20.** US heart transplant survival divided by era of transplant procedure. Patients transplanted in since 2002 have improved survival compared with those transplanted in the prior 2 decades. (Data 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.)

![Functional Status of Surviving Heart Recipients 1995-2006](image)

**Fig. 21.** After cardiac transplantation, many patients regain full function and have no limitations. This result is maintained over time. (Data 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.)
than 5% for subsequent years. Furthermore, improvements in immunosuppressive management have resulted in steadily improving outcomes during the past 2 decades (Fig. 20). The benefits of cardiac allograft transplantation are not isolated to a mortality advantage. Those patients who survive cardiac transplantation also have significant functional benefit. Most of these patients, who preoperatively had NYHA class III and IV heart failure, will function without limitation postoperatively (Fig. 21). A small fraction of patients are actually able to return to employment.

MARGINAL DONOR ORGAN, ALTERNATE LIST TRANSPLANTATION

Occasionally, otherwise well-suited patients may not be eligible for cardiac transplantation based on one or more of the traditional contraindications (see Box 1). These patients, who otherwise would fare well with transplantation, may be offered enrollment in an alternate list transplantation program. Most commonly, these patients are ineligible due to advanced age, but those who are ineligible due to other relative contraindications can also be considered for such programs. Alternate list patients are listed with UNOS, but are offered nonideal organs that have been turned down by standard list recipients. Once an organ has been turned down for all other standard list recipients, it can be considered for alternate list recipients. Usually, alternate list patients receive organs with mild coronary artery disease, positive hepatitis serology, or some degree of LV dysfunction. Because of the secondary risks associated with these marginal donors, it is imperative that these patients be counseled and specifically consented to the alternate list program. Survival after alternate list cardiac transplantation is inferior to standard transplantation, but it is far superior to medical management. These programs enable greater use of donor organs and offer cardiac transplant to recipients who would otherwise be deemed ineligible (Fig. 22).

REFERENCES


73. Martin J, Friesewinkel O, Benk C, et al. Improved durability of the HeartMate XVE left ventricular assist device provides safe mechanical support up to 1 year but is associated with high risk of device failure in the second year. J Heart Lung Transplant 2006;25:384–90.


