HEART TRANSPLANTATION:  
A Thirty-Year Perspective

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Abstract Heart transplantation has evolved over the past 30 years into a mainstay of therapy for heart failure patients. As the surgical technique and basic immunology were defined, heart transplantation became a real therapeutic option. Over the next few decades, thoracic transplant teams at Stanford University and other institutions refined this mode of therapy. This review addresses the history, current surgical technique, recipient and donor selection, postoperative care, immunosuppression, short- and long-term complications, and clinical outcomes associated with this procedure.

INTRODUCTION

Heart transplantation is currently one of the most effective therapies for end-stage heart disease. Although scientists and physicians have faced many challenges in bringing heart transplantation into the therapeutic realm, the fact that most of these challenges have been overcome represents a modern example of the power of medicine. As cardiothoracic surgeons, cardiologists, and basic scientists have worked side by side over the past 30 years, they have brought the surgical techniques, patient care, and immunology involved in this procedure from the bedside to the bench and back to the bedside. Accordingly, heart transplantation has continued to improve the quality of life and survival of heart failure patients.

Recently, the 30-year experience in heart transplantation at Stanford University was reviewed, demonstrating the refinements and evolution of this program from a decade of laboratory work into a clinical program of over a thousand heart transplant recipients (1). From this groundwork sprouted more than 200 heart transplantation centers throughout the world that have carried the torch of progress along with Stanford. This review of the world literature describes the historical aspects of this journey as well as the current state of heart transplantation with respect to surgical techniques, recipient and donor selection, clinical management, and potential pitfalls.
MINIATI • ROBBINS

HISTORY

Although there are accounts of heart transplantation in ancient civilizations, the development of heart transplantation as a real therapeutic option has occurred only in the past 30 years. After the pioneering work of Carrel & Guthrie (2), who demonstrated the ability of the transplanted heart to survive and resume function, several decades passed before any significant advances were made in this arena. Then, the development of cardiopulmonary bypass in the 1950s made heart transplantation a potential reality. During this decade, several groups around the world attempted to refine the technical aspects of transplanting the heart into the orthotopic (normal anatomic) position (3–8). The landmark paper of Lower et al. (9), which conceptualized and refined the atrial cuff technique of orthotopic heart transplantation in dogs, represented a major step forward. This innovation enabled the transplanted heart to adequately support the circulation and allowed the recipient dogs to survive and exercise normally for up to three weeks. Further experiments by this team using this technique resulted in dogs surviving more than one year (10). Concurrent advances in immunology produced a better understanding of the principles of tissue rejection and the role of the immune system in this process.

The first human-to-human heart transplantation was performed by Christiaan Barnard in Cape Town, South Africa, in December 1967 (11), followed by the first successful cardiac transplantation in the United States by Norman Shumway in January 1968 at Stanford University (12). Thereafter, other leading cardiothoracic surgeons from around the world made a flood of attempts at cardiac transplantation. Because of the lag time in discovering appropriate immunosuppressive agents, however, these investigators were forced to perform a nearly impossible balancing act between infection and rejection. The vast majority of attempts from 1967 to 1971 were unsuccessful, and most surgeons abandoned the procedure.

The teams of Norman Shumway, at Stanford University, and Richard Lower, who had moved to the Medical College of Virginia, worked on the principles of heart transplantation virtually alone through the next decade. During this time, they helped to establish recipient selection criteria (13), the use of the endomyocardial biopsy to diagnose rejection (14), the use of rabbit antithymocyte globulin to treat acute rejection (15), and early and late management principles (16). Thanks to the persistence of these teams, heart transplantation is one of the most effective therapies for end-stage heart disease today, and as of March 2000, over 55,000 heart transplantations have been performed (17).

SURGICAL TECHNIQUE

As the use of heart transplantation spread around the world, a number of investigators began to experiment with variations of the conceptually simple technique described by Lower et al. (9). The “Lower and Shumway” or biatrial method consists of anastomoses of the donor left and right atria to those of the recipient
at the midatrial level, allowing short operative time and avoidance of potential complications associated with individual vena caval and pulmonary vein anastomoses (i.e., thrombosis, stenosis) (18, 19). Over time, however, surgeons have found disadvantages of this technique, including enlarged atria with atrioventricular valve insufficiency, impaired atrial contractile function, and associated arrhythmias.

In an attempt to improve function and physiology, surgeons have developed the bicaval and total techniques of heart transplantation. In the bicaval technique (Figure 1), described by Baumgartner et al. (20) and Sievers et al. (21), individual anastomoses of the superior and inferior vena cavae are performed in place of the right atrial cuff anastomosis. The total technique, developed by Yacoub & Banner (22) and Dreyfus et al. (23), includes this modification plus the anastomosis of paired pulmonary veins in place of the left atrial cuff anastomosis. Several studies have compared these methods from both functional and clinical perspectives (see 24 for review). The newer techniques have proven at least as effective as, and in some investigations more effective than, the original biatrial technique with respect to arrhythmia (particularly sinus node dysfunction requiring pacemaker support), valvular function, hemodynamics, exercise capacity, and patient survival. A recent survey of 75% of the world’s heart transplantation centers indicated that the bicaval technique is the most frequently used, and the general consensus among heart transplantation surgeons is that ultimately the bicaval technique will be demonstrated to have clinical superiority (25).

RECIPIENT SELECTION

With the success of heart transplantation came the need to establish strict transplantation candidate selection criteria. Such criteria result in the most prudent allocation of scarce donor organs to benefit the largest number of patients. The most common indications for adult heart transplantation are ischemic and idiopathic dilated cardiomyopathies, together comprising almost 90% of all adult indications (Figure 2). In children, the most common indications include congenital anomalies and myopathy, in varying contributions according to age groups (17). The contraindications to heart transplantation vary somewhat from one center to another, but many include irreversible extracardiac end-organ dysfunction (such as cirrhosis), recent cancer with uncertain status, psychiatric illness with poor medical compliance, severe irreversible pulmonary hypertension, and active infection. Other systemic afflictions, such as diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, and morbid obesity represent relative contraindications.

Determining which heart disease patients should be listed for transplantation should be as objective and judicious as possible. While the number of heart failure patients continually increases, the treatment of heart failure continues to improve. Some patients with severe left ventricular dysfunction remain symptom-free, and
Figure 1  Bicaval orthotopic heart transplantation technique. Above, anterior view of the recipient’s chest after excision of the native heart. Below, anterior view of the transplanted heart partially sewn into place. SVC, superior vena cava; Ao, aorta; PA, pulmonary artery; LAC, left atrial cuff; IVC, inferior vena cava; dotted lines, original position of excised native heart.
Figure 2  Adult heart transplant indications. CAD, coronary artery disease; Misc, miscellaneous; Retx, retransplantation (reprinted from Reference 17 with permission from Elsevier Science).

some studies indicate that for correctly selected patients, medical management can achieve similar symptomatic and survival outcomes as heart transplantation (26, 27). Therefore, as a general rule, evaluation for potential heart transplantation should be instituted only if a contraindication-free patient continues to suffer severe cardiac disability despite optimal medical management.

One screening method that has been used extensively is the measurement of peak exercise oxygen consumption (VO2). Historically, provided the patient could reach the anaerobic threshold, a peak VO2 of $<15$ ml/kg/min or $<55\%$ of predicted peak VO2 has led to strong consideration for listing for heart transplantation. These set points for listing, however, were derived before beta-blocker therapy was available and may need to be adjusted in the future.

Another important functional parameter to measure is pulmonary vascular resistance (PVR). Patients with severe heart failure often have an increased PVR due to their primary illness, and if this problem cannot be managed medically, a newly transplanted heart could suffer acute right-sided heart failure and cause the patient’s immediate demise. Also, increasing PVR has been shown to have a linear impact on one-year and five-year survival rates (17). Optimal PVR for transplantation has been controversial, but most centers accept a value of no greater than 3–4 Wood units with maximal vasodilator therapy, including 100% oxygen, nitroprusside, and inhaled nitric oxide.

Recipient age has been another area of debate among heart transplantation programs. At Stanford, the upper age limit was initially 50 years, and over time this general age limit has been extended to 65 years, although successes have been achieved in carefully selected patients over 70 years old. In addition, the program at the University of California, Los Angeles has instituted an alternative list, including patients up to 75 years old, to receive donor hearts that otherwise might not be used (28). According to the year 2000 Registry of the International Society for Heart and Lung Transplantation (ISHLT), advancing recipient age increases the one-year
and five-year post-transplantation mortality risk, with significance beginning at around age 65 (17). Concurrent studies, however, indicate one-year and four-year survival rates similar to younger patients’ in carefully selected recipients over age 69 (29).

In the end, the decision to list a patient for heart transplantation must be individualized within a general framework of indications and contraindications. Optimal medical management must be achieved prior to making this decision and must be continued while the patient awaits transplantation. Additional psychological and social factors must also be considered, and the final decision should be made by the transplantation team and the patient together.

DONOR EVALUATION

Like recipient selection, the evaluation of potential donor hearts depends on universally accepted objective criteria that may be modified by the particular circumstances and program-based trends within each case. The most common causes of death of organ donors are intracranial bleed, motor vehicle accident, gunshot wound, and closed head injury. Information obtained at the primary screening, which is generally performed by specialists from organ procurement organizations (see listings at www.aopo.org), includes cause of death, body size, ABO blood type, serologies including HIV and hepatitis B and C status, routine laboratory data, and clinical course. A secondary screen conducted by a transplant cardiologist or cardiac surgeon entails evaluation of relevant (particularly thoracic) injuries, baseline electrocardiogram, chest X-ray, arterial blood gas analysis, and echocardiogram. The final screen is performed by the procuring surgeon, who assesses the donor for any signs of deterioration that may have occurred during the organ allocation process and inspects the physical specimen for signs of contusion or other injuries.

Absolute contraindications for using a potential donor, recommended by the American College of Cardiology 24th Bethesda Conference Report on cardiac transplantation (30), include positive HIV status, carboxyhemoglobin level greater than 20%, intractable ventricular arrhythmia, arterial oxygen saturation less than 80%, previous myocardial infarction, severe echocardiographic ventricular dysfunction (ejection fraction less than 10%), and severe coronary artery disease detected by arteriography. Relative contraindications include, among others, positive hepatitis B or C serology, sepsis, history of metastatic cancer, evidence of cardiac contusion, prolonged hypotension, noncritical coronary artery disease, and history of intravenous drug abuse.

Since heart transplantation has become a viable treatment for heart failure, the scarcity of donor organs has been a major difficulty. A combined consensus conference of the American Society of Transplant Physicians and the American Society of Transplant Surgeons was held in March 2001 in an attempt to establish
guidelines for increasing donor organ utilization, and the results of this meeting are to be published in the *American Journal of Transplantation*. One option that has been applied is the use of marginal donors. These hearts generally come from older donors or from young patients with decreased left ventricular function by echocardiogram but with no obvious reason for left ventricular failure. Wheeldon et al. (31) have demonstrated that, in many cases, a donor who is unacceptable by strict physiological criteria can be converted into a satisfactory donor by hormone replacement therapy. The use of this “Papworth protocol” of donor management, with comprehensive monitoring and a cardiac-trained anesthetist on the donor team, has been shown to substantially increase the number of donor hearts without adverse effects on the recipients.

The issue of maximum donor age has been developing over the years. Donors are on average approximately 30 years old, although, in an effort to expand the number of potential donors, many centers will consider donors up to 55 years old. Some studies report the safe and effective use of older donors (32, 33), but the latest ISHLT Registry does cite increasing donor age as a factor that increases the one-year and five-year mortality of transplant recipients in a linear fashion (17). The use of older donors, particularly in teenage pediatric recipients, has been demonstrated to adversely affect long-term outcome (34).

**POSTOPERATIVE CARE**

The immediate postoperative care of heart transplant recipients is similar to that of other cardiac surgical patients. Extubation and weaning from inotropic support are performed as soon as possible, along with patient mobilization and physical therapy. Occasionally, the recipient’s pulmonary vascular resistance is elevated, leading to right-sided failure of the donor heart. This immediate complication has been controlled with inhaled nitric oxide (35, 36), ventricular assist devices (37, 38), and, in extreme cases, extracorporeal membrane oxygenation (39, 40).

Apart from the monitoring and treatment of the patient’s cardiopulmonary functional parameters, most attention is focused on the institution and progression of an immunosuppressive protocol. A triple-drug regimen of cyclosporine (CsA) or tacrolimus (FK506), azathioprine (AZA) or mycophenolate mofetil (MMF), and prednisone is typical, starting with higher doses in the immediate postoperative period and weaning to lower doses as tolerated (Table 1). Kobashigawa (41) recently reviewed immunosuppression for heart transplantation and described the mechanisms and major side effects of these drugs along with several agents that may be used clinically in the future. In particular, FK506 (42) and MMF (43) have shown promise as alternatives to CsA and AZA, respectively, and further studies may elucidate additional long-term benefits of these agents (44). Other agents that have had success in solid organ transplantation and will likely be used for heart transplantation in the future include sirolimus (rapamycin) and monoclonal
TABLE 1  Immunosuppression for heart transplantation protocols

<table>
<thead>
<tr>
<th>Drug</th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone</td>
<td>500 mg IV intraoperatively then 125 mg IV q8hr ×3</td>
<td></td>
</tr>
<tr>
<td>OKT3 induction</td>
<td>5 mg IV/d ×7</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>6–10 mg/kg/d PO or 0.5–2 mg/kg/d IV</td>
<td>3–6 mg/kg/d PO</td>
</tr>
<tr>
<td>Or</td>
<td>Tacrolimus (FK506) 0.15–0.30 mg/kg/d PO</td>
<td>0.15–0.30 mg/kg/d PO</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2 mg/kg/d PO</td>
<td>1–2 mg/kg/d PO</td>
</tr>
<tr>
<td>Or</td>
<td>Mycophenolate mofetil 3000 mg/d PO</td>
<td>3000 mg/d PO</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1 mg/kg/d PO tapered to 0.4 mg/kg/d</td>
<td>0.1–0.2 mg/kg/d PO</td>
</tr>
</tbody>
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*a Reproduced from Reference 68 with permission.
*b Omit if preoperative serum creatinine level is >1.5 mg/dl and use IV.
*c Or as modified by blood levels.
*d Omit if white blood count is <4000/mm³.

antibody interleukin (IL)-2 receptor antagonists such as dacliximab (daclizumab) and basiliximab.

Many centers perform cytolytic induction therapy with polyclonal or monoclonal antilymphocyte antibodies, usually with a 3- to 10-day course beginning immediately after transplantation. Although the bioactivity of these agents is not fully understood, in general they function by causing the lysis of lymphoid cells. The most commonly used preparations are the equine-derived ATGAM and rabbit-derived RATG (both polyclonal) and the mouse preparation OKT3 (monoclonal). Whereas the polyclonal preparations have pan–T-cell activity (anti-CD2, -CD3, -CD4, -CD8, -CD18, and -HLA-DR), OKT3 is directed specifically against the epsilon chain of the CD3-receptor complex of human T cells. Cytolytic induction clearly benefits some groups of patients, including those at high risk of acute rejection (e.g., females, patients with high panels of reactive antibodies) and patients with renal dysfunction (via avoidance of the nephrotoxic effects of CsA) (45). Disadvantages of antilymphocyte antibody therapy include a slight increase in incidence of cytomegalovirus infection, possible increase in development of posttransplantation lymphoproliferative disorder, sensitization/serum sickness, and the “first-dose effect,” which consists of fevers, chills, and mild hypotension (45, 46). In addition, cytolytic induction therapy is more expensive than other modes of induction, although studies have shown that lower doses and shorter courses of administration are as effective as the doses originally used, making this treatment more affordable.
REJECTION SURVEILLANCE

An important aspect of the care of the heart transplant recipient is surveillance for acute rejection. A study by the Cardiac Transplant Research Database Group indicated that the risk for acute rejection normally peaks within the first month after transplantation and then decreases rapidly (47). This report also showed a mean of 1.25 rejection episodes per patient in the first year after transplantation, declining to 0.18, 0.13, and 0.02 in the second, third, and fourth years, respectively. Despite this decline over time, acute rejection continues to cause significant morbidity and mortality in heart transplant recipients, necessitating careful monitoring and prompt treatment.

Because clinical symptoms of rejection are often vague and relatively late in terms of immune cell destruction of myocardial cells, routine testing for rejection in the absence of symptoms is standard procedure. In heart transplants, unlike kidney and liver transplants, there are no reliable serological markers for rejection, although troponin T levels have been suggested as an adjunct (48). In the absence of such a test, the endomyocardial biopsy remains the gold standard method for detecting acute rejection in transplanted hearts. Typically, patients are first biopsied two weeks after the transplantation, then once per week for the next two weeks, once every two weeks for the next eight weeks, once per month for the next three months, and four times per year thereafter. If rejection is detected, patients are treated and then rebiopsied after 10 to 14 days. The uniform criteria established by the ISHLT are described by a scale from 0 to 4 in increasing severity of lymphocyte infiltration and myocyte necrosis (49).

TREATMENT OF ACUTE REJECTION

A standard algorithm for the treatment of acute rejection is shown in Figure 3. Low-grade rejection (ISHLT grade 1A/B or 2) can often be managed with adjustments in the patient’s maintenance regimen or with oral steroids, and there is some debate as to whether these grades of rejection should even be treated. In general, intravenous pulse steroids are the initial line of therapy for higher-grade histological rejection (ISHLT grade 3A/B or 4) or for rejection causing significant hemodynamic compromise (necessitating inotropic agents or mechanical ventricular assistance). If the patient does not respond, has demonstrated steroid resistance in the past, and has not been exposed to the anti–T-cell antibodies, OKT3, RATG, or ATGAM can be used (50). Care must be taken when using these agents because patients may develop antibodies against these animal-derived molecules, leading to decreased effectiveness, serum sickness, and possibly acute vascular rejection with graft loss (46, 51). Another alternative for treating recurrent acute rejection consists of conversion from AZA to MMF and/or from CsA to FK506. Occasionally, a patient presents with persistent,
refractory rejection that is resistant to steroids. For these cases, additional strategies for immunosuppression include total lymphoid irradiation, plasmapheresis, photopheresis, and conversion from AZA to cyclophosphamide or methotrexate (50, 52).

As more options for immunosuppression become available, transplant physicians will be able to individualize each patient’s induction and maintenance regimen to achieve maximum efficacy with minimum toxicity. A patient’s age and gender, renal function, presence or absence of ongoing infection, and predisposition to bone marrow suppression will be important factors to consider.

In addition, as the risk factors and pathophysiology of graft coronary artery disease become more apparent, physicians may be able to tailor each patient’s immunosuppression to prolong the long-term function of cardiac allografts (53).
GRAFT CORONARY ARTERY DISEASE

Although short-term outcomes continue to improve, the long-term success of heart transplantation is still hindered by graft coronary artery disease (GCAD, also known as cardiac allograft vasculopathy and transplant coronary artery disease). According to the most recent ISHLT Registry, 21.7% of heart transplant recipients are afflicted with GCAD five years post-transplantation, and GCAD represents a significant cause of death (17). This accelerated form of coronary artery disease is characterized by diffuse and heterogeneous narrowing of both large-caliber and small-caliber vessels, and although fibrous neointimal hyperplasia is the predominant underlying pathophysiological process, arteritis and atheromatous changes probably also play a role in this disease (54).

Among the many risk factors postulated, those that appear to have the greatest weight are a recipient’s underlying diagnosis of coronary artery disease and increasing donor age, with the five-year odds ratio doubling when donors are 50 years of age or older (17). Other important risks include alloantigen-dependent and alloantigen-independent factors. Alloantigen-dependent factors include donor/recipient histocompatibility (55) and number of acute rejection episodes. Alloantigen-independent factors include donor brain death, recipient cytomegalovirus infection, graft ischemic time, and the myocardial oxidative stress resulting from ischemia and reperfusion of the donor heart. All are believed to play an important role in the development of GCAD (56).

Because of the accelerated nature of this disease process and its associated significant morbidity, early detection is required for any treatment to have a significant response. Because conventional coronary angiography is insufficiently sensitive, intravascular ultrasound (IVUS) has been employed more often for the annual surveillance of heart transplant recipients. IVUS allows for the measurement of intimal area, lumen area, plaque morphology, vessel remodeling, and progression of disease over time (57).

Developing effective therapies for GCAD has been a daunting task. Because of the diffuse nature of the disease, traditional options for coronary artery disease such as bypass grafting and angioplasty have had limited success (58–60). Angioplasty, particularly with stenting (61), can be efficacious for focal lesions, but the restenosis rate may ultimately prove prohibitive. Coronary artery bypass grafting may be performed on carefully selected patients, but perioperative mortality and durability of distal perfusion remain concerns. Retransplantation has also been employed, but GCAD frequently recurs in the retransplanted hearts. In addition, the ethical debate over the appropriateness of allocating a donor heart to an older, previously transplanted patient versus a younger, immunologically naïve patient remains to be resolved.

Ultimately, the key to treating GCAD will probably fall in the realm of prevention. Control or modulation of patient immune responses, environmental influences (lipid profiles, control of diabetes and hypertension, and infections), and
donor-specific factors (pretransplantation injury and antigenicity) may be attained with advancements in donor care, organ preservation, new immunosuppressive agents, and the ultimate objective in transplantation, immunological tolerance of the allograft (54). Until these strides are made, the long-term success of heart transplantation will continue to be limited.

COMPLICATIONS

In addition to GCAD, there are several short- and long-term complications associated with heart transplantation. These problems may be broadly categorized into technical complications and complications of immunosuppression.

Adverse events due to technical difficulties related to the transplantation procedure include superior vena caval stenosis and tricuspid regurgitation requiring valve replacement. Although both complications are rare, with reported incidences of 2.4% (62) and 1.8% (63), respectively, they are worth mentioning because of their associated morbidities. Superior vena caval stenosis is usually related to donor-recipient mismatch of caval diameter and can be treated by operative or percutaneous interventional correction. Tricuspid regurgitation can result from chordal disruption by the biopompe during the endomyocardial biopsy procedure and, if severe, may require surgical replacement.

Complications of immunosuppression include drug toxicities, infection, and neoplasms. All immunosuppressive agents have multiple significant toxicities. Corticosteroids, in particular, can take a serious toll on a patient’s well-being. If patients require relatively high steroid levels, side effects can include diabetes, hyperlipidemia, osteoporosis, peptic ulcers, weight gain, and psychiatric disorders. Among the other most notable adverse side effects of immunosuppression are nephrotoxicity, which may result from CsA and FK506 therapy; diabetes mellitus, with FK506; bone marrow suppression, with long-term azathioprine administration; and gastrointestinal symptoms, with MMF.

Although immunosuppressive agents have become more specific over the past 30 years, infectious complications persist as a major cause of death, especially within the first year after heart transplantation (17). Within the first month of transplantation, infections are usually of nosocomial bacterial origin, including Pseudomonas aeruginosa, Staphylococcus aureus, Enterococci, and Enterobacteriaceae. These organisms can cause pneumonia, urinary tract and wound infections, and bacteremia associated with the use of intravascular devices (64). Later infections are commonly caused by viruses and opportunistic fungi (e.g., Pneumocystis, Candida, and Aspergillus).

Cytomegalovirus (CMV) is probably the most frequently encountered infectious organism, and patients may present with pneumonia, gastroenteritis, hepatitis, or retinitis, alone or in combination. Because of the mortality risk, especially with CMV pneumonia, and the association of CMV with the later development of GCAD, prophylaxis against and prompt treatment of CMV infection cannot be overemphasized. In cases of CMV serological mismatch between the donor and
the recipient, such prophylaxis includes ganciclovir and hyperimmune globulin for six to eight weeks post-transplantation.

Another clinical problem associated with immunosuppression is the development of neoplasms, the most notable of which is post-transplantation lymphoproliferative disorder (PTLD). Other tumors include malignancies of the skin and lips, non-Hodgkin lymphomas, Kaposi sarcoma, and uterine, cervical, vulval, and perineal neoplasms. Frequencies of common adenocarcinomas such as breast, lung, colon, and prostate do not exceed that in the general population (65). The most common first-line treatment of PTLD consists of drastic reduction of immunosuppressive drug doses, and other options range from conventional chemotherapy to antiviral and immunologically based therapies (66).

SURVIVAL

The overall one-year survival rate of heart transplant recipients, according to the ISHLT database, is currently 81%, with a patient half-life (time to 50% survival) of 9.8 years (17), although many centers report over 90% one-year survival. After the first post-transplantation year, the mortality rate is constant at approximately 4% per year. Patients who have received heart transplants within the past five years have one- and three-year survival rates of 85.6% and 79.5%, respectively. Figure 4, displaying data from the ISHLT database, shows the steady improvement in survival from one era to the next in heart transplantation. Approximately 40% of patients are hospitalized in the first post-transplantation year, for infection, rejection, or other causes, and this value drops to 20% by the third and fifth post-transplantation years. Heart transplant patient physical rehabilitation programs are common and

![Survival graph](image-url)

**Figure 4** Adult heart transplant actuarial survival by era. (Reprinted from Reference 17 with permission.)
have been shown to increase a patient’s capacity for physical work (67). The vast majority of patients report no physical limitations, but less than 40% of heart transplant recipients work full-time. This low value may be explained partly by older recipients having reached retirement age and by the fact that for many heart transplant recipients, gainful employment requires sacrificing disability and insurance benefits, without which they could not afford their maintenance medical therapy.

SUMMARY

The field of cardiac transplantation has steadily evolved into a mainstay of therapy for heart failure patients over the past 30 years. Once the major hurdles of the surgical technique and a basic understanding of immunology were cleared, cardiologists, nurses, infectious disease specialists, social workers, cardiothoracic surgeons, and immunologists continued to refine these aspects of heart transplantation while learning more about long-term obstacles. Acute rejection still occurs, but it does not represent a major difficulty for most patients, who enjoy a quality of life that would not be possible without a heart transplant. The holy grail of tolerance may yet be attained, as knowledge of the immune response and the means to control immunity improve. In the meantime, it is hoped that increasingly individualized immunosuppression will continue to decrease the incidence of infectious complications and may also play a role in preventing graft coronary artery disease.

Unfortunately, the success of heart transplantation has only magnified the shortage of donor organs, which will continue to be a tremendous problem. One positive result from this limitation of heart transplantation has been the intense interest generated in other surgical forms of heart failure treatment, including mechanical support, biventricular pacing, mitral valve repair, coronary artery bypass grafting, the Dor procedure (endoventricular circular patch plasty repair), and cell transplantation. Many of these alternatives, in particular mechanical support systems, probably will progress into long-term destination therapy as alternatives to transplantation. As the population of heart failure patients continues to grow, both heart transplantation and these alternative therapies will become more refined, such that heart transplantation may be reserved for those patients who would benefit most from it. We can expect that as donor utilization improves, so will recipient selection, ultimately resulting in further progress in the survival and quality of life of heart transplant recipients.

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