Honoring 50 Years of Clinical Heart Transplantation in *Circulation*

In-Depth State-of-the-Art Review

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ABSTRACT: Heart transplantation has become a standard therapy option for advanced heart failure. The translation of heart transplantation from innovative experiments to long-term clinical success has married prescient insights with discipline and organization in the domains of surgical techniques, organ preservation, immunosuppression, organ donation and transplantation logistics, infection control, and long-term graft surveillance. This review explores the key milestones of the past 50 years of heart transplantation and discusses current challenges and promising innovations on the clinical horizon.

The roots of clinical heart transplantation can be traced to Alexis Carrel in the early 20th century. Carrel was profoundly affected by the death of French President Marie Francois Sadi Carnot in 1894 after being stabbed in the abdomen, resulting in exsanguination from a lacerated portal vein. Carrel's belief that repair of the portal vein could have been lifesaving stimulated an intense interest in vascular anastomoses.[1]

DEVELOPMENT OF SURGICAL TECHNIQUE

After migrating to North America, his seminal collaboration with Charles Guthrie at the University of Chicago began in 1905. Together, they described the technique of transplanting a donor heart within the neck of dogs.[2] Their work on vascular anastomoses resulted in the Nobel Prize in Medicine for Carrel in 1912.

Russian scientist Vladimir Demikhov performed pioneering transplantation experiments in the 1940s and 1950s, including canine heart and heart-lung transplants.[3] Experimental orthotopic (homologous) heart transplantation techniques were reported by Webb et al[4] and Golberg et al[5] in the 1950s. Webb et al[4] initially used anastomotic couplers for pulmonary venous connection; Goldberg et al[5] described a left atrial anastomosis; and Cass and Brock[6] added a right atrial technique.

Others, including Reemtsma and colleagues[7,8] at Tulane University, demonstrated prolonged survival after orthotopic heart transplantation. Stimulated by Reemtsma group's foray into kidney xenotransplantation, James Hardy at the University of Mississippi attempted an ill-fated xenotransplantation of a chimpanzee heart into a dying 68-year-old man in 1964.

The landmark experiments of Richard Lower and Norman Shumway at Stanford, first with canine autotransplantation and then allotransplantation, demonstrated for the first time (1959) that an animal could return to normal recovery with its circulation supported entirely by a transplanted heart.[9]

Kondo and colleagues[10] at Maimonides Medical Center in New York extended canine survival by focusing on puppies. Taking advantage of the immature immune

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system, they achieved survival in 1 puppy of >100 days after orthotopic heart transplantation. Shumway and Kantrowitz were poised for clinical application of heart transplantation when Christiaan Barnard electrified the world with the first human heart transplantation in Cape Town, South Africa, on December 3, 1967 (Figure 1A). Three days later, Adrian Kantrowitz performed the world's first infant heart transplantation on an 18-day-old infant with Ebstein anomaly using the heart of an anencephalic infant. The baby died of acute cardiac failure shortly after the transplantation. Barnard performed the third heart transplantation on January 2, 1968, resulting in the first long-term survivor (18 months). Shumway performed the fourth heart transplantation 4 days later (Figure 1B). Years later, the original technique of biatrial anastomoses (Figure 2A) would be largely replaced by the bicaval method in which the recipient's right atrium is fully excised and the recipient vena cavae are anastomosed to the donor venae cavae. This modification of the transplantation technique resulted in a lower incidence of tricuspid insufficiency and fewer atrial arrhythmias.

Although heterotopic heart transplantation had a long history in the experimental laboratory, it was first used clinically in 1974 by Losman and Barnard. The donor heart was transplanted into the thoracic cavity with the native heart remaining in place.[12] Initially, the donor heart essentially served as a permanent biological left ventricular assist device (LVAD); the technique was later modified to a biventricular support[13,14] (Figure 2B). Heterotopic heart transplantation was used primarily in the 1970s and 1980s, but it is rarely used today because of inferior long-term survival.

ORGAN PRESERVATION

At the time of heart procurement, the donor heart is arrested, and its contractile function resumes after reperfusion in the recipient's body. In the early days, organ preservation was achieved solely by hypothermic storage[15] based on experimental studies of Webb et al[15] and later Shumway's group.[6] In the 1970s, different cardioplegic solutions were developed for use in cardiac surgery and refined for their use in heart transplantation, with the goal of achieving rapid cessation of contractility and reducing the negative impact of ischemia on the heart. Extracellular cardioplegic solutions (eg, St. Thomas solution, Celsior) contain an electrolyte concentration ratio that results in cardiac arrest through inhibition of the Na^+/K^+-ATPase cell membrane pump. Intracellular solutions (eg, University of Wisconsin or histidine-tryptophan-ketoglutarate solution) have a low sodium concentration and a higher potassium content, which lead to cellular depolarization and diastolic cardiac arrest.[17] A recent meta-analysis suggested that organ preservation with University of Wisconsin solution is associated with less ischemic necrosis than Celsior and with better recipient survival compared with histidine-tryptophan-ketoglutarate cardioplegia.[18]

Despite advances in hypothermic organ preservation, allograft ischemic time continues to represent a strong risk factor for posttransplantation mortality, especially when it exceeds 4 hours.[19] This has been the key factor limiting the distance at which heart allografts can be procured and is the reason that routine donor-recipient human leukocyte antigen (HLA) matching has not been practical in heart transplantation.

Continuous perfusion of donor organs was proposed as an alternative to hypothermic organ preservation in the 1980s,[20] but logistical complexity retarded clinical application. Recently, new techniques allowing continuous normothermic perfusion have been tested clinically and show promise to extend safe procurement over long distances (see Current and Future Innovations in the Field of Heart Transplantation).[21]

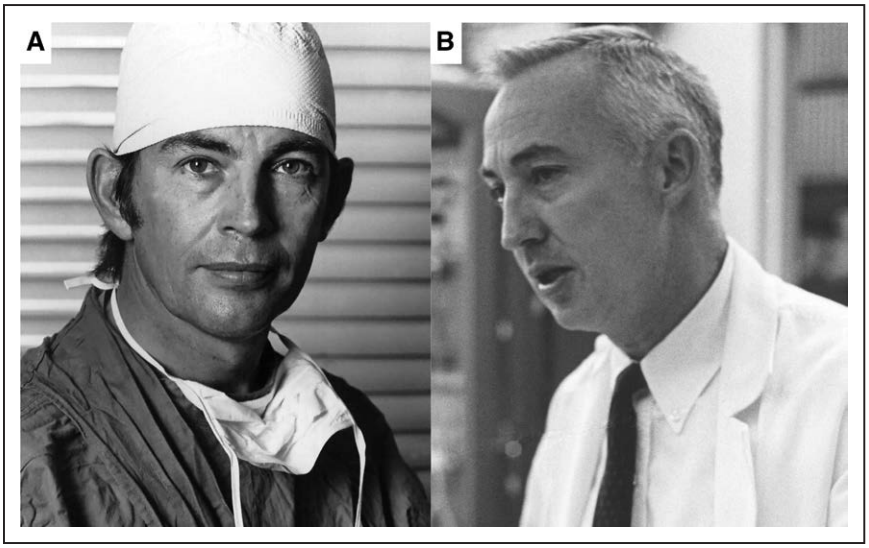

Figure 1. The pioneers of first human heart transplantations.
A, Dr Christiaan Barnard. Figure courtesy of Heart of Cape Town Museum, Cape Town, South Africa. **B**, Dr Norman Shumway. Figure courtesy of Stanford Medical History Center, Stanford, CA.

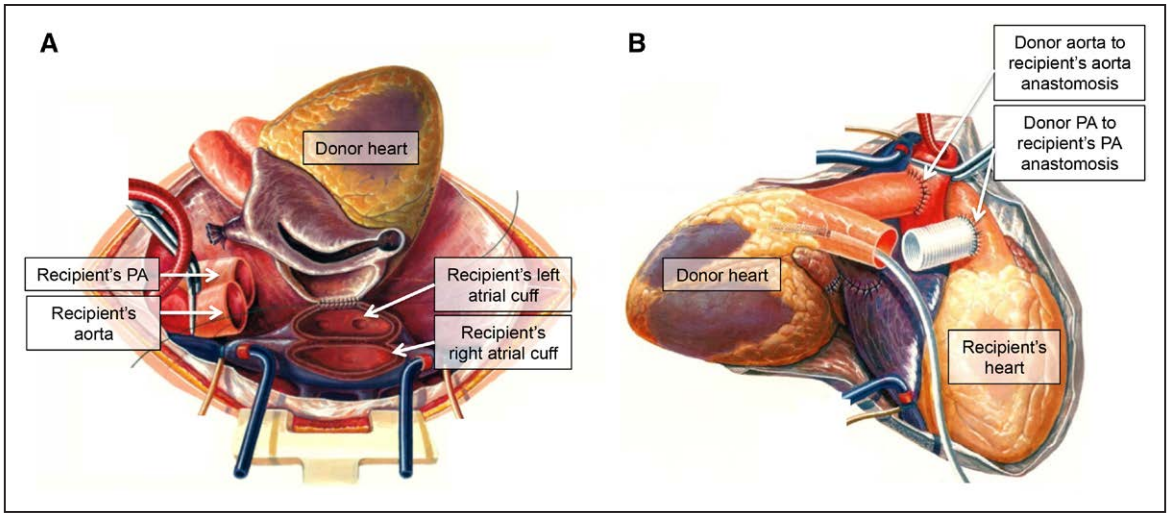

Figure 2. Anatomy of heart transplantation.
A, Orthotopic heart transplantation. The recipient heart is excised except for the cuffs of the recipient's right and left atria. The donor heart is transplanted into the correct anatomic position by anastomosing the donor and recipient right atrium/right atrial cuff, left atrium/left atrial cuff, aorta, and pulmonary artery (PA). A later refinement introduces a bicaval technique whereby the recipient right atrium is fully excised and the recipient vena cavae are anastomosed to the donor right atrium. **B**, Heterotopic heart transplantation. The recipient native heart remains in situ while the donor heart is transplanted into the thoracic cavity. The donor and recipient atria are anastomosed; the donor aorta is anastomosed to the recipient aorta; and the donor PA is anastomosed to the recipient PA. Adapted from Reichart et al[11] with permission. Copyright © 1987, RS Schulz Verlag.

ALLOGRAFT REJECTION

Once the surgical technique and organ preservation allowed reliable execution of the heart transplantation procedure, acute rejection of the allograft became the primary consideration for patient survival. Rejection of the allograft is primarily a T cell–mediated response presenting as acute cellular rejection. Hyperacute rejection and antibody-mediated rejection (AMR) are caused by preformed antibodies against ABO blood group antigens or HLA antigens on the allograft. The original methods to detect rejection (signs of heart failure and electrocardiographic abnormalities) were insensitive and, when present, indicated that the rejection was severe. Philip Caves, a Scottish surgeon visiting at Stanford University, proposed a technique for percutaneous endomyocardial biopsy. His modification of an old Japanese bioptome allowed percutaneous access into the right internal jugular vein and right ventricle, from which small pieces of myocardium could be retrieved for pathological analysis.[22] Pathological assessment of the myocardium was codified by Margaret Billingham and became the gold standard for assessment of graft rejection.[23,24]

Biopsy grading of rejection has focused predominantly on cellular rejection,[24] and a standardized grading scale was proposed by the International Society for Heart and Lung Transplantation in 1990.[25] Over time, challenges in consistent application of the different grades became apparent because the pathological grading did not fully correspond with clinical treatment decisions. In 2005, this formulation was revised and simplified to include the grades of no rejection (0 R), mild rejection (1 R, nondamaging focal or interstitial lymphocytic infiltrates), moderate rejection (2 R, damaging focal or diffuse infiltrates), and severe rejection (3 R, dense diffuse infiltrates with disruption of myocardial architecture);[26] (Figure 3A and 3B). Unless associated with hemodynamic compromise, treatment of acute cellular rejection with high-dose steroids typically results in full resolution of the changes without long-term consequences.

AMR is less frequent but is now an established entity. Circulating antibodies directed against the allograft can cause AMR, leading to endothelial damage, macrophage infiltration, deposition of complement and immunoglobulin, and thrombosis of myocardial microvasculature.[27,28] Non-HLA antibodies might also cause AMR but are not routinely tested for.[27] The pathology diagnosis and grading of AMR include light microscopy (evidence of endothelial swelling and presence of intravascular macrophages) and immunostaining for the presence of complement split products (Figure 3C and 3D).[28] Symptomatic AMR predisposes for a higher incidence of cardiac allograft vasculopathy (CAV) and mortality.

The risk of acute rejection is highest in the first 6 months after transplantation, and most centers perform routine surveillance heart biopsies during the first few months, reducing the frequency thereafter. In the current era of more effective immunosuppressive strategies, the marked reduction in the risk of late cellular rejection has prompted most centers to stop routine surveillance biopsy after 1 to 3 years, although the practice varies among centers.[29]

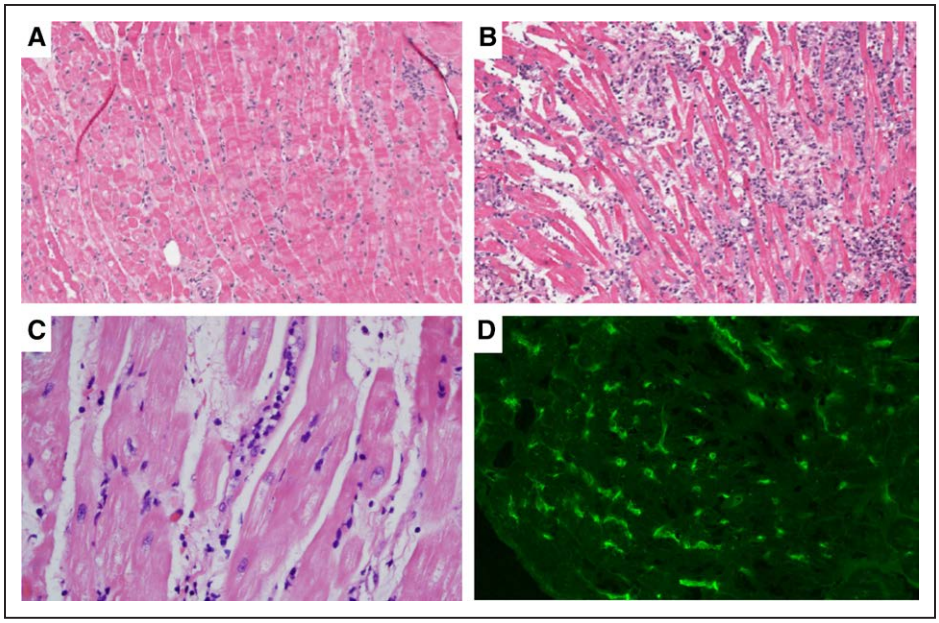

Figure 3. Acute rejection.
A, Mild cellular rejection: focal lymphocytic infiltrate. **B**, Severe cellular rejection: dense lymphocytic infiltrate, myocyte necrosis, and disruption of myocardial architecture. **C**, Antibody-mediated rejection: endothelial swelling and macrophage infiltration in the capillaries. **D**, Antibody-mediated rejection: C4d (complement split product) deposition in perimyocyte capillary walls. **A** and **B**, Hematoxylin and eosin (H&E) stain, ×20 magnification. **C**, H&E stain, ×40 magnification. **D**, Immunofluorescence C4d stain, ×40 magnification. Images courtesy of Patricia Revelo, MD; Elizabeth Hammond, MD; and Dylan Miller, MD.

The limitations of myocardial biopsy include its invasiveness, expense, and considerable interobserver variability in interpretation.[30] Therefore, concerted efforts over the years have focused on developing noninvasive and less expensive alternatives. Unfortunately, the proposed substitutes have had variable success. Use of cardiac imaging, including assessment by echocardiography and magnetic resonance imaging, has so far achieved relatively low accuracy.[31] More recently, gene-expression profiling of peripheral blood mononuclear cells has been investigated with an empirically derived quantitative assessment of mononuclear cell gene expression in peripheral blood specimens.[32] In the multicenter randomized IMAGE trial (Invasive Monitoring Attenuation Through Gene Expression) involving stable, low-risk patients >6 months after transplantation, a proprietary gene-expression profiling test commercially known as Allomap (CareDx Inc, Brisbane, CA) demonstrated a very high negative predictive value, thereby offering a reasonable alternative to routine biopsies.[33] Allomap has since gained regulatory clearance for clinical use to rule out rejection. Its key limitations are a low positive predictive value in the context of its cost and lack of information on AMR.

The search for new methods of rejection surveillance continues. The detection of cell-free DNA of donor origin in recipient blood has been tested as a means to predict rejection in the transplanted heart.[34] Molecular assessment of biopsy tissue examines mRNA expression and compares it with a reference set of RNA expression in specimens of known rejection grades. This technique has proved reproducible in kidney transplantation, and its utility in predicting cellular rejection and AMR in heart transplantation is now under investigation.[35]

IMMUNOSUPPRESSION

Although the surgical challenges of heart transplantation were overcome in the 1960s, interest in the procedure quickly waned because recipients had a high rate of early rejection and mortality. By the 1970s, most major centers abandoned heart transplantation, and it was not until the discovery of cyclosporine that heart transplantation re-emerged to become an accepted treatment for end-stage heart disease. Advances in immunosuppression and perioperative care have dramatically improved survival, with 1-year post-transplant survival of 90% and a median post-transplant survival of >12 years in the modern era (Figure 4).[36]

The host immune response against the allograft necessitates lifelong immunosuppression (Figure 5), striking a delicate balance between modulating the immune system enough to prevent rejection while avoiding the adverse effects of immunodeficiency (infection, malignancy) and drug toxicities (nephrotoxicity, hypertension, hyperglycemia, hyperlipidemia).

The immune system has innate and adaptive mechanisms capable of both recognizing antigens on the allograft and mounting a response. The innate response is the first line of defense and requires no prior sensi-

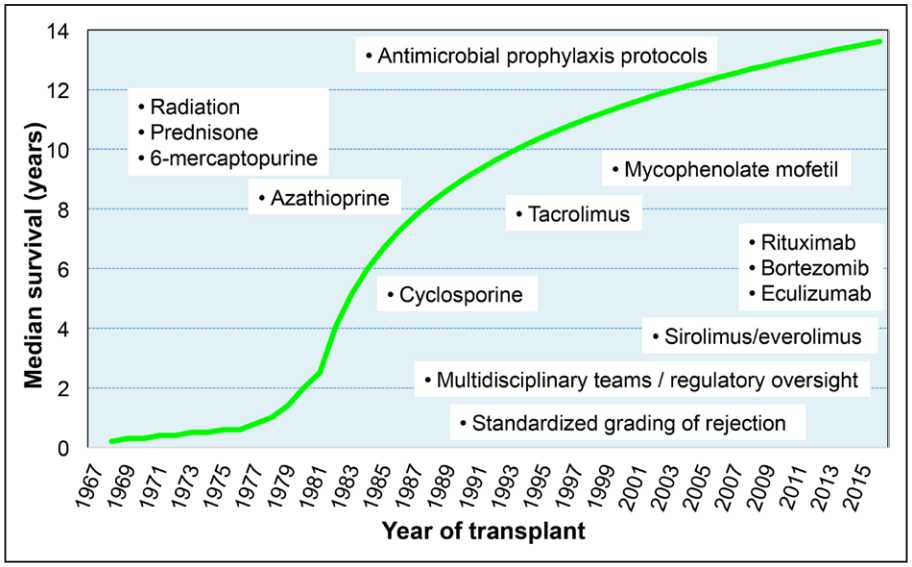

Figure 4. Median survival after heart transplantation and approximate time of introduction of key immunosuppressive agents and standardized clinical care approaches in heart transplantation based on data submitted to the International Society for Heart and Lung Transplantation International Thoracic Transplant Registry.
Median survival between 1968 and 1980 is a best estimate because complete survival information for the early transplantation era is not available. Median survival after 2005 has not been reached, and displayed data represent an estimate based on survival through August 2017. Analysis courtesy of Wida Cherikh, PhD, and Anna Kucheryavaya, MS.

tization. Cells of the innate immune system can activate the adaptive immune response through cytokine release and antigen presentation. The adaptive immune system consists of thymus-derived lymphocytes (T cells) and bursa-derived lymphocytes (B cells). T cells can recognize only antigens that have been processed and bound to major histocompatibility molecules on other cells, including antigen-presenting cells of the adaptive immune system and B cells. Bound antigens stimulate the T-cell receptor, which activates downstream pathways, including the calcineurin pathway, leading to proliferation and production of cytokines such as inter-

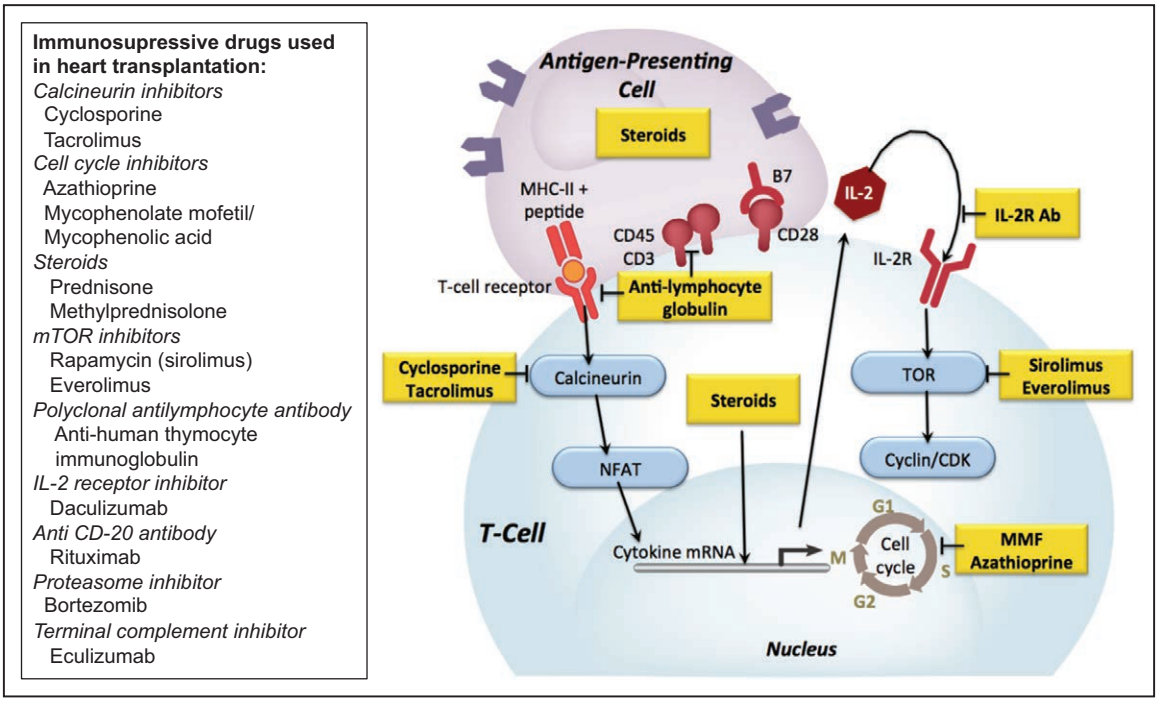

Figure 5. List of immunosuppressive drugs commonly used in heart transplantation and their site of action in the T cell.
CDK indicates cyclin-dependent kinase complex; IL-2R Ab, interleukin-2 receptor antibody; MHC, major histocompatibility complex; MMF, mycophenolate mofetil/mycophenolic acid; NFAT, nuclear factor of activated T cells; and TOR, target of rapamycin.

leukin-2, which promotes clonal expansion of T cells. Helper T cells activate the effector cells of the immune system: natural killer cells, B cells, and cytotoxic T cells.

Immunosuppression strategies have been designed to mitigate the immune response of the recipient against the donor allograft while limiting the toxicity of the individual agents (Figure 5). Immunosuppressive regimens fall into 3 categories: induction, maintenance, and rejection treatment. Induction therapy is an intensive course of immunosuppression given perioperatively that aims to aggressively modulate immunity during this high-risk period. This is particularly useful for the allosensitized patient who carries preformed antibodies against HLA antigens[37] and for the patient with renal impairment where it allows for delayed start of nephrotoxic immunosuppressive drugs. Approximately 50% of heart transplant recipients receive induction therapy, and the most commonly used agents are T cell–depleting agents (anti-thymocyte globulin, alemtuzumab) and interleukin-2 receptor antagonists (basiliximab).[36] Induction therapy may reduce the incidence of cellular rejection and possibly slow the progression of CAV[38] but increases the risk of infection and malignancy.[39,40] The comparative efficacy of induction therapy agents has not been examined in a randomized trial, and no survival benefit has been demonstrated compared with no induction.

After transplantation, most patients are prescribed a 3-drug maintenance immunosuppression regimen consisting of a calcineurin inhibitor (CNI), an antimetabolite, and a tapering dose of corticosteroids. Calcineurin is a calcium-dependent serine/threonine phosphatase that activates nuclear factor of activated T cells, a transcription factor that upregulates the expression of interleukin-2. The CNIs cyclosporine and tacrolimus work by dampening the T-cell response to alloantigens. The efficacy profile of cyclosporine allowed the return of heart transplantation into the clinical mainstream in the 1980s (Figure 4). Tacrolimus has since become the preferred CNI because of lower rates of rejection and a more favorable side-effect profile.[41] The key adverse effects of CNIs are nephrotoxicity, hypertension, dyslipidemia, and hyperglycemia. CNIs are metabolized by the cytochrome p450 system, which is a degradation pathway for numerous drugs, thereby setting the stage for multiple drug-drug interactions.

The antimetabolites azathioprine and mycophenolate mofetil/mycophenolic acid (MMF) interfere with cell growth and division. Azathioprine, a prodrug metabolized into a purine analog, inhibits DNA synthesis in T and B lymphocytes. Adverse effects include leukopenia, thrombocytopenia, and anemia. MMF reversibly inhibits inosine monophosphate dehydrogenase, the rate-limiting enzyme of the de novo guanine synthesis pathway. MMF selectively targets proliferating lymphocytes because they are entirely dependent on the de novo pathway, whereas other cell types can use the salvage pathway. A large clinical trial comparing MMF with azathioprine in heart transplantation showed improved survival and lower rates of rejection for patients treated with MMF.[42] As a result, MMF has almost entirely replaced azathioprine as the preferred antimetabolite.

Corticosteroids were among the first immunosuppressive agents used in transplantation and remain an important component of maintenance regimens because of their potent and diverse anti-inflammatory and immunosuppressive effects. Corticosteroids prevent the production of cytokines, growth factors, vasoactive substances, and adhesion molecules by inhibiting transcription factors such as activator protein-1 and nuclear factor-κB. Long-term corticosteroid use is associated with many adverse effects, including Cushing syndrome, glucose intolerance, infection, and osteoporosis. Patients at low risk for rejection are typically tapered to a low dose or entirely weaned off steroids by 12 months after transplantation.

The proliferation signal inhibitors sirolimus and everolimus inhibit the mammalian target of rapamycin, an important kinase regulating the cell cycle, and thus inhibit proliferation of T and B cells and vascular smooth muscle cells. Sirolimus or everolimus when substituted for azathioprine and used in combination with cyclosporine produce lower rates of rejection and CAV.[43,44] Sirolimus in combination with tacrolimus decreases the rates of treated rejection, cytomegalovirus infection, and malignancy.[45] However, sirolimus worsens the nephrotoxicity of CNIs and delays sternal wound healing and thus should not be initiated immediately after transplantation.[43] Sirolimus used in place of CNI (CNI-free regimen) late after transplantation may improve kidney function in patients with renal impairment.[46] Proliferation signal inhibitors used in place of MMF may reduce progression of CAV, viral infections, and malignancy.[43,44,47]

Although triple-drug regimens are the most common for maintenance immunosuppression, CNI avoidance and CNI monotherapy have been trialed. A small study showed that sirolimus used in place of a CNI is noninferior for rates of rejection and mortality, but further validation is needed.[48] Single-drug immunosuppression with tacrolimus after early withdrawal of MMF and steroids is effective but requires a higher dose and may promote nephrotoxicity.[49]

The treatment of AMR focuses on removing and neutralizing antibodies, inhibiting B cells and plasma cells, and dampening the inflammatory and coagulation pathways.[27] Immunosuppressive agents used for the treatment of AMR include rituximab, bortezomib, and eculizumab. Rituximab is a monoclonal antibody against CD20 antigen present on B cells, which induces prolonged B-cell depletion. Bortezomib inhibits 26S proteasome, which interferes with protein synthesis in plasma cells and eventually leads to plasma cell apoptosis. Eculizumab is a humanized monoclonal antibody that inhibits the C5 component of the complement, preventing formation of the complement membrane attack complex.

Many drug-drug interactions need to be taken into consideration in patients on long-term immunosuppressive therapy. Among the most common are interactions between CNIs and other drugs metabolized by the cytochrome P450 system such as certain antifungal agents, antibiotics, and statins.[50] Other less frequent (and less commonly known) interactions can also take place, and it is therefore a good practice to exclude possible interactions every time a new medication is prescribed in a transplant recipient.

ALLOSENSITIZATION

In 1969, a pivotal study by Patel and Terasaki[51] demonstrated poor outcomes in kidney transplant recipients who had preformed antibodies against donor HLA antigens. In the modern era, the presence of circulating antibodies against the allograft (allosensitization) remains challenging and is associated with worse outcomes for transplantation candidates and transplant recipients.[52] Risk factors for allosensitization include pregnancy, blood product transfusions, previous organ or tissue transplantation, and the use of mechanical circulatory support (MCS) devices.[37] Sensitized transplantation candidates are less likely to find an immunologically compatible donor, spend longer on the wait list, and are at increased risk of AMR after transplantation.[52] Screening for anti-HLA antibodies is routine for all heart transplantation candidates. If clinically significant antibodies are missed, the graft may be subjected to an aggressive humoral response. However, because all screened antibodies do not constitute the same allograft threat, restricting the potential donor pool on the basis of weak or likely irrelevant antibodies may reduce the organ opportunities for a given recipient.[52]

The original approach used for antibody detection was the cell-based complement-dependent cytotoxicity assay, which detects complement-fixing antibodies causing cell injury and death. Alloantibody screening entails adding the transplantation candidate serum to wells containing lymphocytes from a sample of donors. Alloantibodies in the transplantation candidate's serum will bind to corresponding HLA antigens on the donor's lymphocytes and activate the complement cascade, causing lysis of the lymphocytes. In the absence of reactive antibodies, this reaction will not take place. The results are reported as percent panel reactive antibody, a proportion of wells with cells injured by the recipient serum. This test does not differentiate between antibodies against HLA class I and II antigens. The sensitivity of the complement-dependent cytotoxicity assay was later improved with the addition of anti-human globulin to the reaction. More recently, the cell-based flow cytometry cross-match has been used, which is more sensitive than complement-dependent cytotoxicity, quantifies antibody-binding strength, and differentiates between antibodies against class I and II HLAs.

The introduction of solid-phase assays overcame some of the limitations of cell-based assays by increasing the sensitivity and specificity of the testing and providing semiquantitative information on the strength of the antibody. Rather than the use of cells, solubilized HLA antigens are fixed to color-coded microparticle beads identified by variations in fluorescence, and bound antibodies are identified with a flow cytometer or a Luminex platform (One Lambda, Thermo Fisher Scientific, Canoga Park, CA).[53] Single-antigen bead assays, which contain beads individually coated with a specific HLA molecule, have the highest sensitivity and specificity and can identify the HLA subtype against which an antibody is directed.[53] With the use of the information on antibody specificities, a calculated panel reactive antibody can be reported with a calculator containing the frequency of antigens in the donor population.[54] Similar to the original panel reactive antibody assessment, calculated panel reactive antibody provides an estimate of the proportion of the donors against which the transplantation candidate has antibodies.

In the past, sensitized patients required a prospective direct cross-match between donor cells and recipient serum before proceeding to transplantation. This required transport of donor lymph nodes or serum to the transplanting center and consequently limited the geographic area of potential donors. Now that the specificities of the prospective recipients' alloantibodies are known, a virtual cross-match (assessment of compatibility by comparing the donor HLA type with the recipient alloantibody specificities) usually obviates the need for prospective cross-match and expands the donor pool for sensitized patients.[55]

Highly sensitized patients require treatment to reduce the antibody burden and to prevent a humoral response against the allograft after transplantation. Antibodies, B cells, plasma cells, and the complement system are all targets for desensitization therapies. Desensitization strategies include combinations of intravenous immunoglobulin, plasmapheresis, rituximab, and bortezomib.[37] The generally accepted goal of desensitization is to achieve a negative cytotoxic cross-match.[56]

Patients who are not sensitized before transplantation can still produce anti-HLA antibodies against the allograft after transplantation, which are known as de novo donor-specific antibodies. Almost half of all patients will develop anti-HLA antibodies within 15 years after transplantation.[57] De novo donor-specific antibodies, especially when detected >1 year after transplantation, are a risk factor for rejection, CAV, graft dysfunction, and mortality. Most centers will treat de novo donor-specific antibodies only if there is evidence of graft dysfunction.

POSTTRANSPLANTATION SURVIVAL AND PATIENT QUALITY OF LIFE

The median survival of adult patients transplanted after the year 2000 exceeds 12 years, which represents

a marked survival benefit compared with continued medical therapy for New York Heart Association stage IV heart failure.[18] The median survival of patients in this cohort who survive the first posttransplantation year is expected to reach 15 years. The median survival in pediatric heart transplantation is even longer, with >70% of recipients alive at 10 years after transplantation.[58]

Early after transplantation, the main causes of mortality include primary graft dysfunction, rejection, and infection. Later after transplantation, the leading causes of death include CAV, nonspecific graft failure, malignancy, and renal dysfunction.

An important goal of transplantation is to regain favorable quality of life and active lifestyle in patients with advanced heart failure. After the acute postoperative period, the majority of patients undergoing heart transplantation do not require hospitalizations, the functional status of 80% of heart transplant recipients is described as ≥80% on the Karnofsky Score (range, 10%–100%),[18] and other aspects of health-related quality of life are also improved significantly compared with before transplantation.[59] Many heart transplant recipients return to work, although securing of healthcare coverage can represent an obstacle for those seeking employment after heart transplantation.

POSTTRANSPLANTATION SURVEILLANCE AND COMPLICATIONS

Long-term posttransplantation care is directed at preserving optimal graft function and minimizing the risk of complications that result from the immune response of the recipient against the graft (rejection, CAV) and the effects of long-term immunosuppressive therapy (infection, hypertension, diabetes mellitus, renal dysfunction, malignancy).

Cardiac Allograft Vasculopathy

CAV is a frequent long-term complication of heart transplantation and a leading cause of late mortality. Despite improvements in immunosuppressive drugs, the incidence of CAV has decreased only marginally, affecting up to 50% of recipients within 10 years of transplantation.[36] In contrast to atherosclerotic plaques of native coronary artery disease, CAV manifests as a diffuse, pan-arterial thickening of vessel intima. CAV can affect the entire length of the epicardial vessel and typically extends to the microvasculature. On histology, epicardial and intramyocardial vessels show concentric intimal thickening, migrated smooth muscle cells, foamy macrophages, and lymphocytic infiltrates. Unlike in atherosclerotic coronary disease, thrombotic occlusion of the vessel lumen in CAV is rare.

The pathogenesis of CAV is complex, with immunological and nonimmunological factors contributing. The donor arrest, organ procurement, and allograft ischemia and reperfusion can all trigger inflammation and endothelial injury. Both innate immunity and adaptive immunity contribute to the development of CAV. During implantation, the donor heart sheds HLA antigens and heat-shock proteins, which can be processed by recipient antigen-presenting cells, leading to activation of T cells. Endothelial cells lining allograft vessels are the primary source of antigens activating the host immune system. Donor-specific antibodies can form against HLA or non-HLA antigens (vimentin, anticardiac myosin) in the allograft. Immune system activation leads to the release of proinflammatory cytokines, further vascular inflammation, and endothelial damage, all of which contribute to the pathogenesis of CAV in the form of myxoid changes in the intima in early lesions and fibrotic and hyalinized changes in advanced lesions.

CAV also shares many of the risk factors associated with native coronary artery disease, including hypertension, hypercholesterolemia, and diabetes mellitus.[60] Other risk factors unique to CAV include cytomegalovirus infection, older donor age, and explosive brain death in the donor.[60,61]

The denervated transplanted heart prevents recipients from experiencing ischemic pain. Patients with CAV can be asymptomatic for some time or have nonspecific symptoms of fatigue, nausea, or abdominal discomfort. By the time the patient presents with reduced left ventricular ejection fraction and heart failure symptoms, the prognosis is typically poor. Therefore, close monitoring of the allograft for early signs of CAV is essential. The mainstay of CAV surveillance is serial coronary angiography, which will typically demonstrate diffuse stenoses in large epicardial vessels and reduction of smaller coronary branches (peripheral "pruning"; Figure 6). Because CAV often occurs along the entire length of the vessel, CAV may be missed or underestimated by angiography alone. Intravascular ultrasound is a more sensitive method that can reliably detect intimal changes (Figure 6). An increase in maximal intimal thickness of ≥0.5 mm on intravascular ultrasound from baseline to 1 year after transplantation is prognostic for poor outcomes and the development of angiographic CAV within 5 years.[62] Negative vessel remodeling is another important feature of CAV that can be assessed on intravascular ultrasound. This is a paradoxical decrease in vessel volume despite intimal thickening. Negative remodeling of the left anterior descending artery on intravascular ultrasound at 1 year after transplantation is an independent risk factor for death or retransplantation.[63]

Noninvasive alternatives to screening angiography include dobutamine stress echocardiography, positron emission tomography, and computed tomographic angiography.[64,65] Proposed biomarkers for increased risk of CAV include C-reactive protein, serum brain natriuretic peptide, troponin I,[61] and possibly serum microRNA 628-5p.[66]

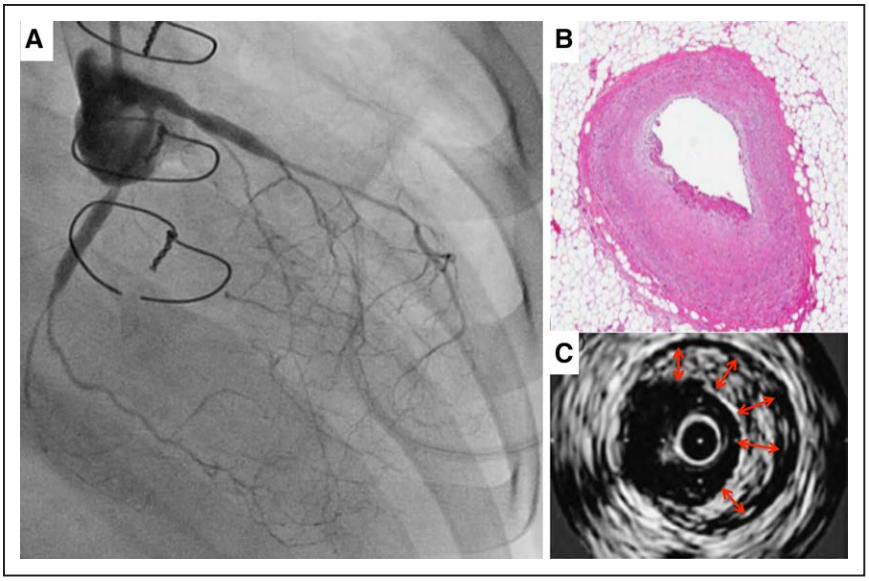

Figure 6. Cardiac allograft vasculopathy (CAV).
A, Angiographic appearance of severe diffuse CAV. **B**, Histological examination of an epicardial coronary artery showing diffuse intimal proliferation. **C**, Severe intimal proliferation (arrows) seen on intravascular ultrasound.

Once CAV develops, current treatments are often ineffective, so prevention is important. The statins pravastatin and simvastatin started early after transplantation decrease the incidence of CAV.[67,68] Pravastatin may provide additional protection by inhibiting natural killer cells.[67] Vitamins C and E may also slow the progression of CAV.[69] Aspirin is typically prescribed daily because of its established benefits in native coronary artery disease. Once CAV is detected, the introduction of a proliferation signal inhibitor such as sirolimus or everolimus can slow disease progression.[44] Clinically significant CAV can be palliated with percutaneous coronary interventions for focal disease, but restenosis rates are high.[70] Retransplantation is often the only viable option but raises questions about equitable organ allocation.

Infection

Because immunosuppression will place the transplant recipient at higher risk of infection, specific interventions aimed at mitigating this risk take place even before transplantation. It is recommended that transplantation candidates have all age-appropriate vaccinations administered.[71] This includes immunizations against pneumococcal pneumonia, tetanus, hepatitis A and B, influenza, and varicella/*Herpes zoster*. This is to ensure an appropriate immune response to vaccinations before posttransplantation immunosuppression blunts the immune response and makes the vaccinations less effective. Use of live vaccines will typically be contraindicated after transplantation because even the attenuated viruses used for vaccination can cause disease in the immunosuppressed host. Screening for and treatment of latent tuberculosis is also recommended before transplantation.

Perioperatively, antibacterial antibiotic prophylaxis is typically used with drugs active against the usual skin flora, especially *Staphylococcus* species.[72] The combination of piperacillin/tazobactam and vancomycin is commonly used and continued for 2 to 4 days after transplantation. Protocol-based antimicrobial treatments are also started shortly after heart transplantation with the goal of preventing opportunistic infections at the time of the highest level of immunosuppression. Various approaches are currently in place for the prevention of cytomegalovirus reactivation, including the use of intravenous gancyclovir and oral valgancyclovir, typically for 3 months after transplantation and longer in the highest-risk patient group (cytomegalovirus-positive donor/cytomegalovirus-negative recipient). Prophylaxis against *Pneumocystis jiroveci* pneumonia is also routine and includes sulfamethoxazole/trimethoprim therapy, with dapsone or inhaled pentamidine as alternatives. Antifungal prophylaxis against mucocutaneous candidiasis may include topical nystatin liquid (swish and swallow), clotrimazole lozenges, or prophylactic-dose fluconazole. Additional specific antifungal prophylaxis may be useful in endemic areas.[73–75]

Antimicrobial prophylaxis protocols have evolved over the years, and their meticulous implementation has greatly reduced the incidence of opportunistic infections that used to result in significant morbidity and mortality in the early posttransplantation period. Although the use of selective antimicrobial prophylaxis and advances in immunosuppression have reduced the risk of infectious complications after heart transplantation,[76] infections remain an important cause of posttransplantation mortality. Approximately 3% of transplant recipients die of infection in the first postoperative year, which represents one third of the deaths in this time period. Approximately 8% of heart transplant recipients succumb to infection within 20 years of transplantation.[18] The leading infections resulting in mortality are bacterial pneumonia, fungal infections (aspergillus, coccidiomycosis, nocardia), and cytomegalovirus.

Hypertension, Diabetes Mellitus, and Renal Dysfunction

Hypertension, diabetes mellitus, and renal dysfunction are frequent posttransplantation comorbidities, and their aggressive treatment reduces the morbidity and mortality associated with these conditions. The incidence of severe renal dysfunction after heart transplant has decreased over the past 20 years, likely a result of strategies aimed at renal function preservation as described in Immunosuppression.

Malignancy

The increased risk of malignancy after transplantation relates to long-term exposure to immunosuppressive therapies and increases with time since transplantation. Careful age-appropriate screening for malignancy is done at the time of transplantation evaluation and is continued after transplantation. The leading posttransplantation malignancy is skin cancer, seen in >20% of patients within 10 years of transplantation. There is higher incidence of cervical, hepatobiliary, and renal cell carcinoma and lymphoma. Posttransplantation lymphoproliferative disorder is a specific type of lymphoma seen in organ transplant recipients. Posttransplantation lymphoproliferative disorder diagnosed early after transplantation is typically associated with Epstein-Barr virus infection, whereas posttransplantation lymphoproliferative disorder late after transplantation is considered a complication of long-term immunosuppression.

MECHANICAL CIRCULATORY ASSIST IN THE CONTEXT OF HEART TRANSPLANTATION

MCS devices have had a major impact on the field of heart transplantation. Durable bridge-to-transplantation (BTT) devices include total artificial heart and ventricular assist devices. A number of temporary mechanical support devices are also used as BTT.

Total Artificial Heart

The first total artificial heart as a BTT was performed by Dr Cooley in Houston in 1969. The patient underwent orthotopic heart transplantation 2 days later but died after 32 hours of renal failure and pneumonia.[77] In 1982, DeVries at the University of Utah implanted the first total artificial heart (Jarvik 7) intended as permanent therapy.[78] This device, now called the SynCardia total artificial heart (SynCardia, Tucson, AZ), has since received approval from the US Food and Drug Administration for BTT use. The leading indication for its use today is severe biventricular failure not amenable to partial mechanical support of the left ventricle.

Ventricular Assist Devices

The original goal of a partial artificial replacement heart, later known as LVAD, was to aid recovery of the heart after complex cardiac surgery.[73] In 1966, DeBakey first used an LVAD in a patient unable to wean from cardiopulmonary bypass after valve surgery.[79] In the 1970s, Portner and Oyer at Stanford University developed an electric dual pusher-plate Novacor LVAD (World Heart Corp, Oakland, CA), resulting in the first long-term survival of a patient with an LVAD[80] and successful clinical use as BTT therapy.[81] Subsequently, the HeartMate I (Thoratec Corp, Pleasanton, CA) intracorporeal pulsatile pump became the first device approved for long-term destination therapy.[77]

Current generations of LVADs use predominantly continuous-flow technology, which allows a marked reduction of device size and a reduction or elimination of moving components such as valves and bearings. This has in turn resulted in improved pump durability (some patients now remain on LVADs for many years), increased patient survival, and reduction of complications. A number of devices have received US Food and Drug Administration approval for use as BTT (HeartMate II [Thoratec Corp, later Abbott, Abbott Park, IL], HVAD [Heartware Inc, FL, later Medtronic, Minneapolis, MN]), and others are undergoing clinical testing (Jarvik2000 [Jarvik Heart Inc, New York, NY], HeartMate3).[82–84] BTT approach with the current-generation devices leads to 6-month survival in the range of 80% to 90% and to a low risk of mortality on the transplantation waiting list (Figure 7).[85]

Another advantage of axial-flow or centrifugal pumps is the possibility of less invasive implantation; the pump itself is implanted via a small left anterolateral thoracotomy, possibly reducing the risk of compli-

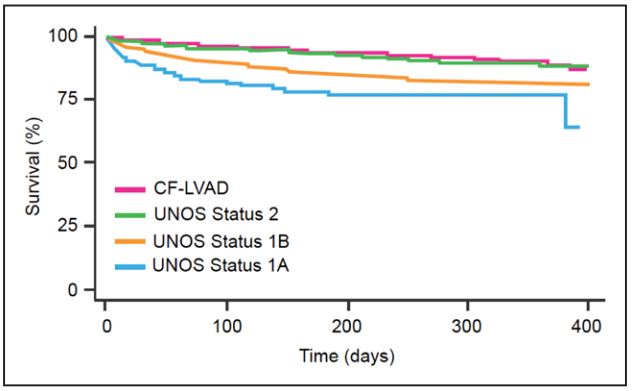

Figure 7. Waiting list survival of heart transplantation candidates registered on the United Network of Organ Sharing (UNOS) waiting list in 2008 to 2011.
UNOS status 1A, 1B, and 2: candidates without mechanical circulatory support listed in high, intermediate, and low urgency status, respectively. CF-LVAD indicates continuous-flow left ventricular assist device. Adapted from Wever-Pinzon et al[85] with permission. Copyright ©2013, American Heart Association, Inc.

cations associated with a full resternotomy at the time of transplantation.[86]

Important post-LVAD adverse events include stroke, infection, gastrointestinal bleeding, and device thrombosis. Future technology improvements are focused on increased biocompatibility of the materials, further miniaturization, artificially generated pulsatility, and conversion to totally implantable systems.

Temporary Circulatory Support

Temporary circulatory support is increasingly applied to patients in cardiogenic shock awaiting or considered for transplantation. Venoarterial extracorporeal membrane oxygenation is a frequently used support system that allows transportation of patients in shock to tertiary heart failure centers. Percutaneous axial flow left ventricular support devices (eg, Impella; Abiomed Inc, Danvers, MA) can be inserted through the femoral or subclavian artery (via surgical access) and provide support to the left ventricle, propelling up to 5 L of blood per minute from the left ventricle into the aorta. Surgically implanted extracorporeal pumps (eg, CentriMag, Abbott) can also be used in the LVAD or right VAD configuration. Despite adequate hemodynamic support, survival after transplantation in patients with temporary circulatory support is often inferior to that of other patient cohorts.

ORGAN ALLOCATION

The early years of cardiac transplantation were challenged by the lack of a uniform definition of death that would allow ethically suitable procurement of donor organs. In 1968, a committee at Harvard University developed a formal definition of irreversible coma,[87] setting the stage for the development of uniform criteria for brain death, which would allow the procurement of living organs from a nonliving patient based on the determination of brain death. During the ensuing years, minor refinements of these criteria were used in the United States to establish the Uniform Determination of Death Act in 1980. With the knowledge that graft survival after cadaver renal transplantation was improved with a more closely genetically matched donor and recipient, organ sharing between regions began in the 1960s, eventually culminating in the establishment of the United Network of Organ Sharing (UNOS) in 1977. The National Organ Transplant Act of 1984 established a national organ procurement and distribution network for organ transplantation throughout the United States.

HEART TRANSPLANTATION FROM THE GLOBAL PERSPECTIVE

During the early 1980s, the need for an organized international forum for the exchange of scientific information to improve patient outcomes provided the stimulus for creating the International Society for Heart Transplantation, later renamed the International Society for Heart and Lung Transplantation. The complex logistics of heart transplantation and the involvement of a wide range of clinicians have contributed to the development of integrated multispecialty teams, a model that has been replicated in many countries. The International Society for Heart and Lung Transplantation International Thoracic Transplant Registry, which receives data from ≈500 heart transplantation programs in 40 countries, reported a continued increase in the annual number of heart transplantations performed worldwide over the last decade (Figure 8).[18]

The number of transplantation candidates placed on waiting lists worldwide typically greatly outweighs the number of available donor organs. In the absence of a reliable prognostic score for stage D heart failure and in combination with the evolving MCS options, it has been difficult to design an organ allocation system that would reliably prioritize transplantation in patients with the greatest need. The recently proposed revisions of allocation systems are intended to readjust some of the current allocation shortcomings.[88,89]

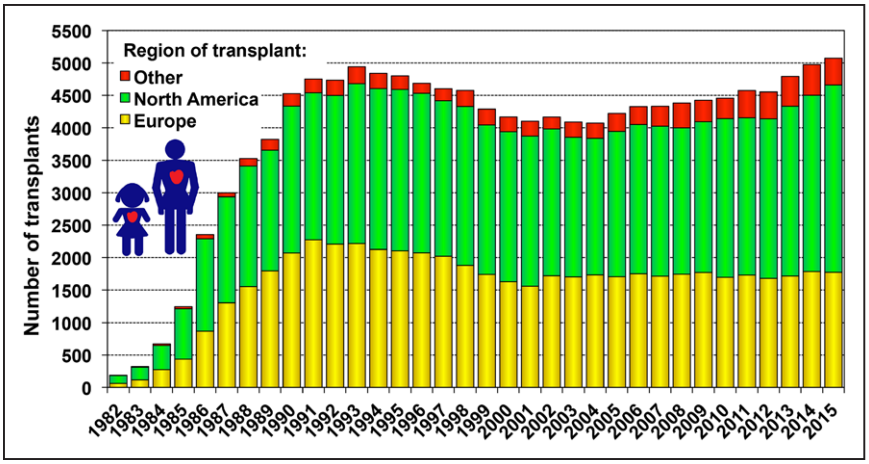

Figure 8. Number of heart transplantations (adult and pediatric) by year and geographic region. Reproduced from Lund et al[19] with permission. Copyright ©2017, Elsevier, Inc.

In some instances, transplantation tourism (seeking a transplantation in country other than the recipient's residence) takes place under circumstances of organ procurement and the transplantation process in violation of the ethics standards of the Declaration of Istanbul.[90] Efforts to reduce the need for transplantation tourism should include interventions that increase the rate of altruistic organ donation and enhance the quality of donor management and the efficiency of the transplantation system as a whole.[91] The eventual goal is for all countries to be self-sufficient as far as availability of donor organs for their citizens.

CURRENT AND FUTURE INNOVATIONS IN THE FIELD OF HEART TRANSPLANTATION

The past 50 years of clinical transplantation have seen continued advances in the care of heart transplant recipients and a concomitant improvement in survival (Figure 4). The perfection of surgical techniques, modern immunosuppressive therapies, avoidance of a hostile immune environment for the allograft, and implementation of rigorous transplant care protocols have all contributed to better outcomes.[18] The key innovations being pursued in the field can be broadly classified as investigations aimed at increasing the availability of donor organs and approaches aimed at improving the long-term survival of patients after heart transplantation.

Ex Vivo Organ Perfusion

Ex vivo perfusion of donor hearts is being actively investigated as a means of increasing the number of organs suitable for transplantation. Rather than being stored in an arrested and hypothermic state, donor hearts are preserved in a warm, beating state. This approach has now been tested clinically in the PROCEEDII trial (Randomized Study of Organ Care System Cardiac for Preservation of Donated Hearts for Eventual Transplantation), in which the 30-day posttransplantation survival was similar with standard storage techniques and with ex vivo perfusion.[92] These favorable results open the opportunity to test ex vivo perfusion as a platform to assess or even improve the quality of organs in which questions about the suitability of the allograft are raised at the time of procurement. Furthermore, if it can be demonstrated that the organs can be perfused for extended periods of time without compromising the viability of the allograft, this could have major implications on how heart allografts could be allocated in the future in the absence of geographic restrictions related to acceptable transportation time.

Donation After Circulatory Death

Another approach likely to expand the current donor pool is heart transplantation using allografts from donation after circulatory death in which organs for transplantation are procured after circulatory cessation in severely ill but not brain-dead donors after the withdrawal of life-sustaining care. The first heart transplantations performed in the 1960s were technically donation after circulatory death transplantations, being done before establishment of brain-death criteria, but until recently, there has been very limited use of donation after circulatory death in heart transplantation,[93] related to both ethics considerations and the concern for injury to the allograft during donor hypotension after the withdrawal of life support. This obstacle is now being addressed through the technological advances in ex vivo perfusion. Investigator teams in Australia and the United Kingdom have reported successful clinical application of this approach.[21,94]

ABO-Incompatible Heart Transplantation

ABO-incompatible heart transplantation has been introduced to clinical care by West et al.[95] ABO-incompatible heart transplantation usually results in hyperacute rejection caused by preformed recipient serum antibodies directed against blood-type antigens of the donor. However, infants do not produce these antibodies for the first ≈6 months of their life. The investigators implemented successful protocols for peritransplantation and posttransplantation care of infants undergoing ABO-incompatible heart transplantation. These protocols have now been adopted by multiple countries and have allowed expansion of the scarce donor pool for infants awaiting transplantation.

Immune modification to allow ABO-incompatible heart transplantation in older children and adults is currently underway.[96]

Xenotransplantation

Xenotransplantation explores transplantation of organs between different species. Leonard Bailey at Loma Linda University performed the first cardiac xenotransplantation in 1984, transplanting a baboon's heart into an infant with hypoplastic left heart syndrome. The baby survived 12 days, dying of multiorgan failure but without evidence of rejection. In part as a result of public outcry against the use of primates, Bailey never performed another xenotransplantation.

In the past few decades, a small number of clinical kidney and liver transplantations using nonhuman primate grafts have been performed. The function of the transplanted organs has been limited to only days or weeks, a result of a powerful response of the human

immune system against the nonhuman donor antigens, not overcome by the standard immunosuppression. However, the greatly improved genome-editing techniques that allow speedy genetic modification of antigen expression in animal models have resulted in renewed interest in xenotransplantation with a porcine model. Preformed circulating serum antibodies in humans that react with the swine leukocyte antigens, proteins of the major histocompatibility complex of the pig, used to represent a strong immune barrier. Recently, knockout pigs that lack major swine leukocyte antigen genes have been engineered, producing animals that do not express 3 key nonhuman swine leukocyte antigens. This reduced the immunogenicity of these organs in a human recipient.[97] Anti-HLA antibodies may still cross-react with other antigens expressed on the porcine cells, but additional genetic modification may soon diminish this problem.

In a heterotopic heart transplantation model, knockout pig to nonhuman primate allograft survival of up to 945 days has been demonstrated. This required higher-than-standard immunosuppression, including maintenance with anti-CD40 antibody. Disappointingly, survival of orthotopic pig to nonhuman primate heart transplantation grafts has so far been limited to <2 months, mostly as a result of perioperative cardiac xenograft dysfunction, which is believed to be distinct from acute rejection.[98]

Another concern in xenotransplantation is the risk of infection transmission. Maintenance of donor animals in pathogen-free facilities may reduce the risk of bacterial, fungal, and exogenous viral infection. All pigs also carry endogenous retroviruses, yet so far, there has been no documentation of transmission of the retroviral genetic material from pigs to nonhuman primates through xenotransplantation.[99]

Although a number of biological and logistical issues remain to be resolved before pig to human heart transplantation can be undertaken, recent calls for clinical testing of pig to human kidney transplant provide a reason for optimism.

Organ Engineering

The immune and infectious challenges faced by xenotransplantation could be circumvented by organ engineering. The proof of concept of this approach was demonstrated by Ott et al.[100] These investigators first generated decellularized extracellular matrix scaffolds of rat hearts by removing cellular tissue from the organs. These scaffolds then provided biomechanical and topographical support for autologous neonatal cardiac cells that repopulated this scaffold.[100] The recellularized hearts showed some automatic contractility and responded to medications. Before this approach can come closer to the clinic, a number of obstacles that would translate this model to a functional bioartificial organ need to be resolved.

Immune Tolerance

In addition to finding new sources of donor organs, improvement of long-term survival remains a priority in heart transplantation. Key improvements in post-transplantation survival in the past decades have been limited predominantly to the first posttransplantation year.[18] However, long-term survival past the first year after transplantation, while markedly better compared with medical treatment of stage D heart failure, is still lower compared with a healthy population. Historically, there have been high expectations that long-term survival will be improved by new immunosuppressive medications, anticipated to provide adequate levels of immunosuppression and a more favorable side-effect profile. Nevertheless, none of the immunosuppressive regimens introduced after CNIs and MMF have been shown to reduce mortality in heart transplantation.

An alternative approach to refining the effect of immunosuppressive therapies would be to reduce the need for immunosuppression through the induction of tolerance of the recipient's immune system to the donor antigens. The main approaches that have shown potential of inducing immune tolerance have been T-cell costimulation blockade (prevention of T-cell activation by donor antigens), mixed-chimerism strategies (recipient bone marrow engraftment with donor bone marrow cells), transient profound T-cell depletion (elimination of recipient T cells at the time of transplantation), and regulatory T-cell approaches (infusion of expanded donor regulatory T cells).[101] Although many of these approaches have induced tolerance in small animal models, translation of these findings to humans has so far not been successful.

Molecular Diagnostic Methods

In the absence of marked qualitative advances in immunosuppressive pharmacotherapy or clinically applicable induction of immune tolerance, it is possible that there are reserves in personalization of the current treatments to individual patients. A recent report by Wever-Pinzon et al[102] highlighted this issue through examination of the leading causes of death in 52 995 heart transplant recipients. The authors showed that there was a strong relationship between the age at transplantation and the hazard of cause-specific death. Patients transplanted at a younger age were several times more likely to die of acute rejection, CAV, and nonspecific graft failure, whereas recipients transplanted at an older age were more likely to die of malignancy and infection. These data suggest that younger patients may be relatively underimmunosup-

pressed and older patients are more likely to suffer the consequences of overimmunosuppression. Indeed, most protocols tailor the level of immunosuppression to time since transplantation. However, truly individualized adjustment of the level of immunosuppression based on the risk of rejection and risk of immunosuppression-related adverse events is challenging to implement. It has been proposed that this level of personalization may be possible with molecular diagnostic techniques. Gene-expression profiles of rejection-related genes in peripheral white blood cells (Allomap test described earlier), both as individual values and in the assessment of their stability over time, have been shown to provide prognostic information related to clinical events.[33,103] Similarly, gene-expression profiles in myocardial tissue have been shown to segregate into distinct archetypes correlated with the probability of acute cellular rejection, AMR, and nonrejection.[35,104] Although the current use of this information is related mainly to decisions about the treatment of acute rejection, these tests could in the future provide a platform for individualized adjustment of the level of maintenance immunosuppression.

Once innovation in the MCS space generates devices requiring less intensive patient and caregiver involvement coupled with better long-term survival, new questions will arise about how to best combine durable MCS with heart transplantation to optimize patient survival and quality of life in the long term. Thus, approaches that will include intermediate- to long-term use of MCS followed by heart transplantation or, alternatively, heart transplantation followed by MCS once the functional graft lifetime is exhausted will undoubtedly be examined.

SUMMARY

Society and the medical community recognize that heart transplantation restores longevity and favorable quality of life in appropriately selected patients with advanced heart failure. Although accurate, this conclusory comment fails to depict the real fabric of this amazing adventure. After more than half a century of concatenations of novel and sometimes heretical experimentation, there followed a nexus of pioneering spirit, opportunity, and an attitude of carpe diem that propelled the protagonists toward that prize of the first human heart transplantation. After the initial epoch of darkness during the 1970s, the subsequent conflation of concepts, discipline, intellectual peptides, and disruptive innovations drove a prodigious multidisciplinary effort that revolutionized the medical options for advanced heart failure. However, many challenges and opportunities remain for the prepared minds embracing this field. The many innovations on the clinical horizon indicate that the next 50 years promise to be no less captivating.

DISCLOSURES

Dr Reichenspurner has served as a consultant for Medtronic, Inc. Dr Kobashigawa has received research grants and/or research support from Novartis, CareDx, and TransMedics. Dr Stehlik has received research support from Abbott, Inc and has served as consultant for Medtronic, Inc. Drs Hunts and Kirklin report no conflicts.

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FOOTNOTES

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