Device Therapy and Cardiac Transplantation for End-Stage Heart Failure

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Abstract: The prevalence of heart failure is increasing, and the prognosis of end-stage heart failure remains dismal. The gold-standard therapy in end-stage heart failure remains cardiac transplantation at the present time, but there is a great excess of eligible candidates compared with the number of donor organs. Advances in mechanical support, the development of the left ventricular assist device (LVAD), and the total artificial heart has reduced mortality and morbidity in patients awaiting transplantation, and LVADs are now approved as an strategy for destination therapy. Miniaturization, increased device durability, and complete implantability may render LVADs an option in earlier stages of heart failure, as a bridge to myocardial recovery or even as a viable alternative to transplantation. Alternative strategies under investigation are cell therapy and xenotransplantation. In the present article, current and potential future therapeutic options in end-stage heart failure are reviewed. (Curr Probl Cardiol 2010;35:8-64.)

Background

An estimated 5.7 million people carry a diagnosis of heart failure in the USA (2006 figures), and almost 300,000 people die of heart failure in the USA each year.[1] The prevalence of heart failure is increasing and increases with age.[1] In the Western world, most heart failure is related to coronary disease, and although the survival of patients post acute myocardial

infarction has improved, this has resulted in an increase in the numbers of patients ultimately developing heart failure.[2] In fact, coronary artery disease presents at an earlier age, predominantly related to the increased prevalence of cardiac risk factors (type 2 diabetes mellitus, hyperlipidemia, hypertension, and obesity) in developed societies.[3] Advances in medical therapy have resulted in improved survival in patients with moderate and severe heart failure, but the prognosis for end-stage heart failure patients remains poor.[4-6] The result of this is a change in the demographics of heart failure patients in recent years, and the increased survival of patients with heart disease into older age. Therefore, the age of patients presenting with advanced heart failure is increasing.[7,8] Although the greatest survival benefit in patients with end-stage heart failure is seen with cardiac transplantation, the supply of donor hearts is limited and therefore not an option for many patients because of age and other comorbid conditions. There has therefore been considerable interest in alternative forms of cardiac replacement therapy, either as temporary bridges to transplantation or as a definitive destination strategy. Current work in this field can be looked at in four spheres: ventricular assist devices, the total artificial heart, cell therapy, and xenotransplantation. At the present time, however, cardiac transplantation remains the gold standard of cardiac replacement therapy.

Device Therapy

A Brief History of Mechanical Support in Cardiac Failure

The development of cardiopulmonary bypass technology in the 1950s was the landmark achievement that greatly assisted the development of more permanent means of mechanical cardiac support.[9] The first known mechanical support device dates back to Russia in the 1940s with the work of Dr. Vladimir Demikhov, who successfully implanted an artificial heart into a canine model, which supported the animal for over 5 hours.[10] The first successful mechanical support device in humans was implanted by Dr. Michael DeBakey at the Texas Heart Institute in 1966. Early devices were large and cumbersome devices that were external and provided temporary support only. However, technological progress has permitted the design and production of smaller devices that have bridged patients toward transplantation. As most congestive heart failure is due to left ventricular failure in adults, these smaller devices were designed to preferentially support the left ventricle, and for the pump itself to be fully implantable, albeit requiring an external source of power. Hence the term left ventricular assist device or LVAD was coined. US Food and Drug Administration (FDA) approval of these devices as bridge to transplant in

the 1990s led to additional trials to explore their potential as long-term support. This is discussed in more detail below.

Temporary mechanical support technology has also advanced, and the miniaturization of these devices has permitted their use with less operative morbidity and more rapid functional recovery following surgery. At the present time a broad range of temporary mechanical support options are available. The most comprehensive mechanical support available for both the systemic and the pulmonary circulation is still best provided by extracorporeal continuous membrane oxygenation for extremely ill patients with pulmonary and cardiac failure, which remains a cumbersome and invasive but extremely effective form of short-term mechanical support.[11] However, the development of devices such as the Impella and the TandemHeart has allowed less invasive forms of temporary support of the systemic circulation typically applied during high-risk percutaneous intervention procedures, such as aortic balloon valvuloplasty and high-risk coronary artery stenting,[12-14] and in cardiogenic shock.[15-17] Larger external pulsatile pumps such as the Abiomed 5000 and the newer magnetically levitated centrifugal Centrimag pump are used to provide temporary support of either the left or the right ventricles or both as a short-term rescue strategy post cardiotomy or as a bridge to more long-term cardiac replacement therapy or recovery.[18-21]

Counterpulsation technology remains a mainstay of acute care in patients with cardiogenic shock, both before and after surgical or percutaneous intervention. This technology has also been developed and miniaturized for potential long-term use in ambulatory patients, most notably the Akpulsor (Cardiak, Ltd, Oxford, UK), C-Pulse (Sunshine Heart, Inc, NSW, Australia), and CardioPlus (Cardioplus, Inc, Detroit, MI, USA) devices. However, to date, none of these devices have been evaluated in an FDA- or Conformité Europeene (CE)-approved clinical trial. Last, enhanced external counterpulsation therapy has been established as an effective form of therapy in intractable angina in non-revascularizable patients with coronary artery disease. The counterpulsation principle and marked left ventricular afterload reduction that results from this completely noninvasive strategy may also be helpful in congestive cardiac failure[22-25] and this has been evaluated in the Prospective Evaluation of EECP Trial.[23,24,26,27]

Ventricular Assist Devices as Long-Term Cardiac Replacement Therapy

At the present time, the gold standard of long-term cardiac replacement therapy remains cardiac transplantation, but the number of cardiac
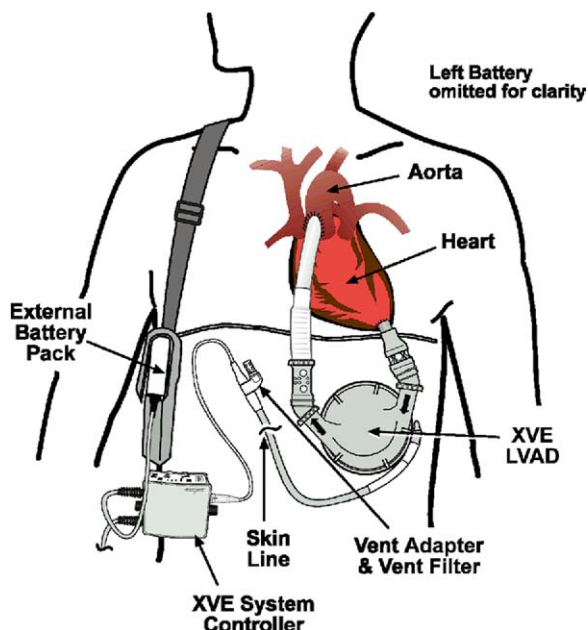
FIG 1. The original LVAD design—the Heartmate XVE. All currently implanted LVAD devices have an inflow cannula that drains the left ventricular apex, and blood entering the body of the pump is expelled through an outflow conduit, usually fashioned of Dacron, which is anastomosed in an end-to-side fashion to the ascending aorta. For the Heartmate XVE, the main body of the pump is implanted within in the abdomen, but smaller pumps such as the Heartmate II may have the pump body within the thorax, or even in the left ventricular apex itself as for the Jarvik 2000. Current devices approved or under evaluation in the USA have an external power supply and controller connecting to the pump via a driveline, which usually exits through the abdomen. For the Heartmate XVE, an additional pneumatic line exists that houses a changeable air filter and also permits external hand pumping in case of device failure. (Color version of figure is available online.)

transplants performed is limited by donor organ availability.[28] Research in genetic engineering and xenotransplantation using transgenic animals as donors has progressed considerably but not yet to the stage of clinical trials.[29] Although considerable progress has been made in the understanding of stem cell biology in heart failure, which may ultimately lead to cellular therapy being an option for the treatment of end-stage heart failure, the field is still in its infancy. Therefore, there has been great interest in the development of LVADs as destination therapy for end-stage chronic heart failure.

Left Ventricular Assist Devices

LVADs have been in use as a bridge to cardiac transplantation for over 20 years, and the Heartmate XVE device (Thoratec Corporation, Pleas-
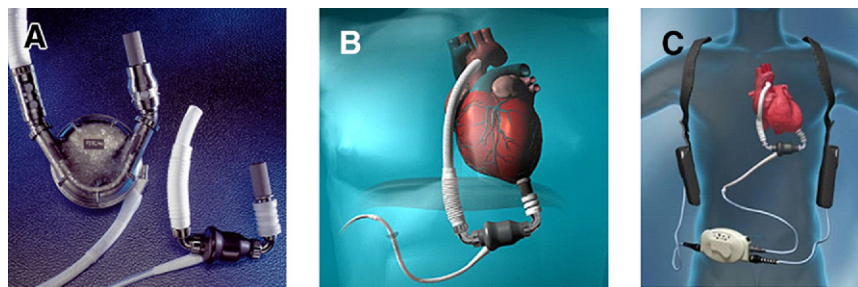
FIG 2. Current FDA-approved LVAD devices in use, Heartmate XVE and the Heartmate II. (A) The Heartmate II device (right) is very much smaller than its predecessor, the Heartmate XVE (left). (B) Its smaller size enables it to be placed in an intra-abdominal or entirely intrathoracic position. (C) It connects externally to a controller and battery pack or external console, as for the XVE. (Color version of figure is available online.)

anton, CA) was approved by the FDA for this purpose in 1994 (Fig 1).[30] Favorable outcomes with LVADs in this role led to these devices being evaluated as potential long-term strategies for cardiac replacement therapy.[30] The Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure (REMATCH) study evaluated the long-term benefit of Heartmate XVE placement compared with optimal medical therapy in end-stage heart failure patients.[5] A 48% reduction in death from all causes was attributable to LVAD therapy compared with best medical therapy in this trial, and on this basis, the Heartmate XVE was approved for use as destination therapy in 2002. To the present day, this pulsatile flow device remains the only device approved in the USA for this indication, but trials are in progress evaluating newer second-generation axial-flow pumps for this indication (see below).

LVADs—History and Evolution. The artificial heart program commenced at the National Institutes of Health in 1964.[31] The first successful cardiac-assist device in humans was implanted by DeBakey at the Texas Heart Institute in 1966 and was later refined and known as the BCM-Rice pump, after Rice University, where it was developed. At the same time, the Kantrowitz group in New York developed an alternative form of LVAD, culminating in their dynamic aortic patch device, first implanted in 1971 and known today as the Kantrowitz Cardiovad.[32] Further technological developments led to the pulsatile LVAD design pioneered in 1976 as the Axio-symmetrical and Pierce-Donachy LVADs. A refined version of the latter device known as the Heartmate (Thoratec) was approved by the FDA as a bridging device to cardiac transplantation in 1994 with the updated version, the Heartmate XVE (Fig 2A), approved as

bridge therapy in 1998. In 2002, following the positive results of the REMATCH trial comparing this device to best medical therapy in patients with end-stage heart failure, it was also approved by the FDA for destination therapy.[5] In the USA, the pulsatile LVAD remains the only design licensed by the FDA for destination therapy at present (Heartmate XVE). Follow-up studies since REMATCH[33] have shown that uptake of LVAD therapy has been poor because there is an unacceptably high incidence of device failure.[34] In addition, Lietz's work shows that there continues to be a very high early mortality with a continued decrement in survival later. Although REMATCH showed that LVAD implantation improved survival compared with medical therapy, both groups had an extremely high early mortality, and most were on inotropic support. This underlines the importance of patient selection. In this respect, Lietz showed that using a novel operative risk score encompassing severity of heart failure, nutritional status, renal function, and RV function, the patients with the lowest risk had the best early survival.[33] However, even in the sickest patients, LVAD therapy offered a significant survival advantage, as shown in a subsequent substudy of the REMATCH population[35] and in a recent study with the Novacor device (also a pulsatile device) in inotrope-dependent patients with end-stage heart failure.[36]

Unlike pulsatile pumps such as Heartmate XVE, a continuous flow pump based on either axial or centrifugal rotors could be made smaller and more durable. Furthermore, continuous flow pumps could be converted easily to totally implantable system. These types of axial-flow devices have been in development since 1988 and first implanted in humans trials 10 years later. The advantage of these devices is their smaller size and also fewer moving parts, which should increase durability. Concerns about nonphysiological nonpulsatile output from these devices in possible end-organ damage have been allayed by recent data showing their safety in relatively long-term use as a bridge to transplantation when compared with pulsatile devices.[37] An important issue with axial-flow devices is their requirement for anticoagulation and the risk of thrombosis and hemolysis. The most commonly used axial-flow device, the Heartmate II device (Fig 2B), is already FDA-approved as bridge therapy to cardiac transplantation in the USA. However, FDA approval has yet to be granted for these devices as long-term destination therapy, pending the results of ongoing head-to-head trials with pulsatile devices, although they have been successfully used in this capacity in other countries.[38] A totally implantable LVAD, the Lionheart device (Arrow

Inc), is also approved as destination therapy in Europe. The absence of an external drive-line may reduce significantly the risk of infection associated with LVAD therapy.[39]

Biventricular Support. The LVAD alone may be unsuitable for patients with advanced congestive cardiac failure with concomitant right ventricular (RV) failure. Often, RV function improves after placement of an LVAD, when RV dysfunction has developed secondary to chronic pulmonary venous congestion, but occasionally persistent right heart failure only becomes apparent after LVAD implantation.[40] In particular, in the setting of intrinsic RV myocardial dysfunction due to ischemic heart disease or infiltrative disease, RV support may prove necessary, with or without additional LVAD support. Recently, risk factors have been identified that may help to better predict patients with ongoing RV failure after LVAD implantation.[41] Traditionally, biventricular support has been with pulsatile pumps, which usually required the use of large and cumbersome external support devices that have required patients to remain in hospital. Recently, portable pneumatic drivers for these paracorporeal devices have been developed for patients to be living in a setting away from the hospitals.[42]

Current Devices in Clinical Trials. In the USA, cardiac-assist devices that are already approved and being evaluated in clinical trials have been implanted under the somewhat artificial designations of either as a bridge to transplantation or as a destination therapy (Table 1). In reality, a significant number of patients who were thought to be poor transplant candidates initially became reasonably good candidates for cardiac transplantation when their multisystem organ dysfunction improved with effective hemodynamic support on ventricular assist device (VAD) therapy. In addition, LVAD implantation as a bridge to cardiac transplantation permits effective exercise capacity[43] and weight loss, improvement in end-organ perfusion, and even reversal of pre-existing medically unresponsive pulmonary hypertension.[44] However, presently it is an FDA requirement for the designation to be made to permit enrollment in a clinical trial. This is not a requirement in the European Union or Australia, where devices approved for use in those regions may be implanted under the broad indication of therapy for advanced cardiac failure.

Currently, the only device FDA approved in the USA as destination therapy is the pulsatile Heartmate XVE device (Thoratec). The Heartmate II destination therapy trial is randomizing patients with advanced congestive cardiac failure in a 2:1 ratio to either Heartmate II or Heartmate XVE, respectively, as destination therapy. This trial commenced enroll-

TABLE 1. LVADs currently under evaluation in clinical trials

Device name	Manufacturer	Device type	Approval status
Heartmate XVE	Thoratec, CA	First generation (pulsatile)	FDA approved in US as DT and BTT
			European CE mark approved for all indications
Heartmate II	Thoratec, CA	Second generation, axial flow	FDA approved in US as BTT
			Under evaluation in Heartmate II DT trial with 2:1 randomization against Heartmate XVE
			European CE mark approved for all indications
Jarvik 2000	Jarvik Heart, NY	Second generation, axial flow	Under evaluation in US as BTT
			European CE mark approved for all indications
VentrAssist	Ventracor, Sydney, Australia	Third generation, centrifugal	Under evaluation in US as BTT
			European CE mark approved for all indications
			Approved for use in Australia
Incor	Berlin Heart, Germany, EU	Third generation, centrifugal	European CE mark approved for all indications
			Not yet under evaluation in US
HVAD	HeartWare, Sydney Australia	Third generation, centrifugal	Under evaluation in Europe for CE mark
DuraHeart	Terumo Heart, MI	Third generation, centrifugal	European CE mark approved for all indications
			Not yet under evaluation in US
Synergy	Circulite, DE	Micro-pump	Under evaluation in Europe for CE mark
			Not yet under evaluation in US

ment in February 2005 and is still currently enrolling patients. The primary outcome data collection is scheduled for June 2009, with a study completion date of June 2011. The Jarvik 2000 axial pump has been under evaluation since April 2005 as a bridge to cardiac transplantation in an FDA-approved multicenter trial and has a scheduled completion date of April 2009 (Fig 3A). The Ventrassist device (Ventracor, Sydney, Australia) (Fig 3C) is a centrifugal pump with a hydrodynamic-bearing mechanism and has been under evaluation since June 2007 regarding its safety as a bridge to cardiac transplantation in an FDA-approved multicenter trial. It has an estimated study completion date of June 2010.

With increasing experience with VAD therapy, other interesting clinical and laboratory observations have been made. Myocytes at subcellular and
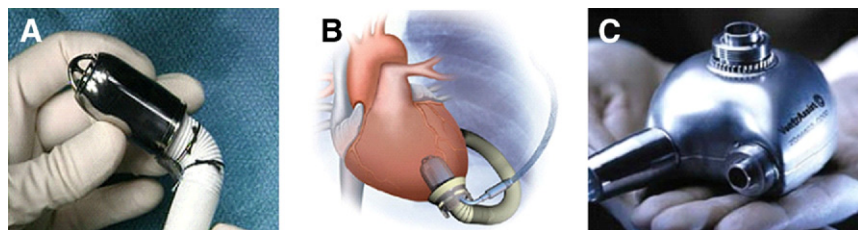
FIG 3. LVADs under FDA evaluation, the Jarvik 2000 and Ventrassist devices. (A) The Jarvik 2000 is 1 of the smallest implantable devices available, the pump itself shown in the figure being implanted entirely within the left ventricular apex (B). (C) The Ventrassist is a third-generation centrifugal pump with a hydrodynamic bearing system, and therefore, a single moving part, which is expected to greatly increase the longevity of the device. (Color version of figure is available online.)

cellular levels as well as the heart as an organ displayed some ability to recover function. This is an interesting and exciting area of research. Yacoub et al (unpublished data) have reported a single-center experience on the very promising possibility of clinically meaningful myocardial recovery. This multicenter FDA-approved trial, the Harefield Recovery Protocol Study, which aims to evaluate the role of the Heartmate XVE device combined with clenbuterol therapy in inducing sufficient LV recovery to allow device explantation, is underway. Recruitment commenced in March 2007 and the final data collection for assessment of the primary outcome is scheduled for January 2010. The study is expected to be completed in August 2010.

Patient Selection. The landmark findings of the post-REMATCH data published by Lietz et al in 2007 highlighted the importance of nutritional parameters, hematological abnormalities, and markers of RV failure and end-organ dysfunction in determining mortality post LVAD placement.[33] These findings brought new perspective to interpretation of the findings of the original REMATCH trial, in that much of the early mortality (up to 30 days postoperatively) could have been attributable to patient selection, as these patients were uniformly New York Heart Association class IV, with severely low cardiac indexes (mean, 1.9 L/min/m^2) and evidence of end-organ dysfunction (mean serum creatinine, 1.7 mg/dL). Specifically, in Leitz's analysis univariate analysis of the post-REMATCH data, highly significant predictors for 90-day mortality post LVAD placement were thrombocytopenia ($<$148,000/μL), low serum albumin $<$3.3 g/dL as a measure of nutritional deficiency, elevated AST $>$45 U/mL reflecting liver congestion, and low hematocrit $\leq$34%. These findings have led to an increased awareness that the previous practice of LVAD implantation as

a last resort in severely decompensated patients is not in the patient's best interest, and that either LVADs should be considered earlier in the evolution of advanced heart failure, when nutrition and end-organ function are still optimal, or means should be undertaken to improve these factors preoperatively where possible. In regard to the latter, where patients still present in advanced decompensated heart failure due to the acuity of illness (eg, post myocardial infarction cardiogenic shock or acute myocarditis), or because LVAD therapy had not been previously considered in more chronic cases, many groups take steps to optimize end-organ function, hematological parameters, and nutrition preoperatively with the addition of inotropic and/or intra-aortic balloon pump support in an intensive care unit/critical care unit setting for some days before scheduling surgery.

Whether LVADs are implanted as destination therapy or as a bridge to transplant, full commitment from the patient and optimal support from family or other caregivers is essential. In this respect, the psychological and sociological milieu of the patient is critical and requires detailed assessment by specialized staff before LVAD implantation, as is routinely true in the consideration of patients for cardiac transplantation.[45-47]

Complications Post LVAD Placement. The main complications specific to LVAD placement distinct from other forms of cardiac surgery are related to driveline infection, postoperative bleeding, and thromboembolism.

Driveline infections are common, and serious, if allowed to progress to pump pocket infection, which can only be eradicated definitively by LVAD explantation.[48] These issues underline the critical importance of patient and care compliance with driveline exit site care. Although intuitively, the larger driveline of the pulsatile devices (eg, Heartmate XVE) compared with the smaller driveline of continuous flow devices (eg, Heartmate II) would be expected to be associated with more driveline infection, recent data have suggested that the risk of infection is probably equivalent.[49] Hopes that total implantability of assist devices and the elimination of a driveline would reduce the risk of infection may be realistic based on recent reports of the Lionheart experience in Europe.[39]

Increased perioperative mediastinal bleeding and spontaneous hemorrhage (commonly gastrointestinal or epistaxis and rarely intracranial) have been associated with LVAD placement, more than what would be expected based on the anticoagulation regimen alone. Some of the increased gastrointestinal bleeding may be attributable to the formation of arteriovenous malformations, which may be more common with continuous flow devices.[50] Recent data have shown that the increased bleeding tendency overall may be largely attributable to acquired platelet dysfunc-

tion due to high shear rates and abnormal microaggregate formation, and in this regard, resemble an acquired von Willebrand's disease.[51,52] Perioperative treatment of these patients with agents such as tranexamic acid may be helpful.[51]

The incidence of neurological events and thromboembolism post LVAD placement is low (<20%) for both pulsatile and nonpulsatile devices, and for the Heartmate II, prolonged periods of low or even no anticoagulation due to bleeding concerns may be safe.[53-55]

RV failure post LVAD placement is associated with increased perioperative morbidity and mortality but is difficult to predict. Work is ongoing to define better means of assessing the need for RV support post LVAD placement and some recent data are encouraging in this regard.[41]

Other complications seen frequently post LVAD placement are exudative pleural effusions, usually left sided or bilateral.[56] These effusions occasionally interfere with patient rehabilitation post LVAD placement, and radiologically guided drainage is effective and safe.

The Total Artificial Heart

Total artificial heart (TAH) technology has evolved simultaneously with the development of LVADs. The first successful implantation in an animal model took place in 1957; the subject, a dog, survived just 90 minutes but this was a landmark achievement. The first human subject was implanted by Cooley of the Texas Heart Institute in 1969. The patient, a 47-year-old male with end-stage ischemic cardiomyopathy, was successfully bridged to transplant for 64 hours. The patient subsequently expired 32 hours post transplantation from overwhelming *Pseudomonas pneumoniae*. Joyce and his team at the University of Utah subsequently developed the Jarvik-7 Total Artificial Heart, which was first implanted in 1982.[57] The patient survived 112 days. Several subsequent implants took place in different centers, the longest recorded survival being 620 days. However, due to unacceptable morbidity and mortality as well as very poor quality of life while on TAH support, the Jarvik-7 was no longer approved by the FDA for production from 1990 onward. The updated version, the Cardiowest TAH (Symbion) (Fig 4A), is still under evaluation—initial results have been encouraging in its safety and efficacy as a bridge to transplantation.[58] The AbioCor device (Texas Heart Institute) (Fig 4B), which is completely implantable with electrical power transferred transcutaneously via internal and external coils, is also being evaluated in clinical trials.[59,60]

Partial Support and Miniaturization—Extending VAD Technology to the "Less Sick." In many respects, VAD technology has advanced with
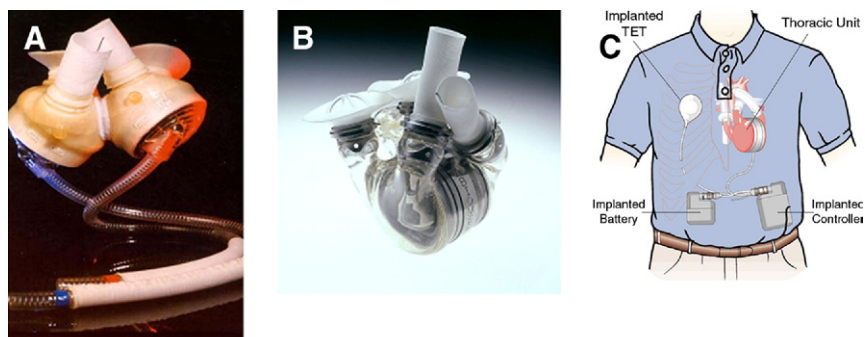
FIG 4. Total artificial heart devices currently under evaluation. (A) The SynCardia Cardiowest is a direct descendent of the original Jarvik-7 TAH (B) The AbioCor (Abiomed) is a similar design that is completely implantable (C). (Color version of figure is available online.)

a view toward engineering devices that would be small, totally implantable, and durable for years as a long-term cardiac replacement. The achievement of this goal is the driving force behind current destination therapy trials with VADs. At the present time, the most promising features surfacing in current technology are third-generation magnetically levitated impeller devices with fewer moving parts (just one) and increased durability, and transcutaneous power delivery, which is expected to considerably reduce driveline-related device infection.

However, there is great interest in the applicability of this technology to a group of patients with advanced heart failure but not as ill as studied in the REMATCH trial. The REMATCH and post REMATCH trial data reflect a population of patients with very advanced disease (New York Heart Association class IV) with significant comorbidities. Most patients were supported by inotropes and many had significant renal dysfunction. Later analysis by Lietz and coworkers demonstrated how these factors negatively affected the long-term outlook of these patients post LVAD implantation.[33] Rendering DT therapy at an appropriate stage of patients' heart failure before they worsened to the point of being moribund would be critical to the improved outcome both in survival and in quality of life. As new devices prove to be more patient friendly and durable, shifting the target population to a less ill group would be in the best interest of patients suffering from advanced heart failure. Patients with less severe heart failure are also less likely to require less output from these devices and that they would only be required to function in a pure "assist mode." The potential need for a device with an output of only up to 2-3 L per minute renders it conceivable to miniaturize the devices themselves and
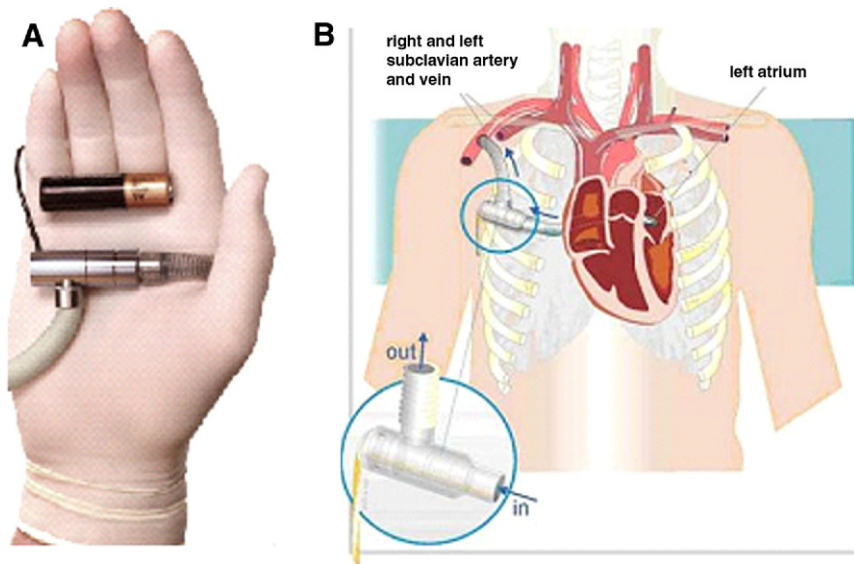
FIG 5. Miniaturized devices. (A) The Synergy (Circulite) device delivers up to 3 L per minute of blood flow but is no larger than a AA size battery. (B) The device is implanted as shown, drawing blood from the left atrium and expelling it into the subclavian artery. (Color version of figure is available online.)

also the route of access required for their implantation. In addition, their lower power requirements also facilitate the development of totally implantable power supply units. Currently, many companies are developing technology for this application, most notably Circulite, Inc, whose Synergy device (Fig 5) requires minimally invasive access to implant the device, which delivers up to 3 L blood per minute to the aorta via the left subclavian artery and has a completely implantable power supply. Devices of this kind with minimal morbidity related to implantation have already been used successfully as a bridge to cardiac transplantation,[61] may potentially alter the course of disease in advancing heart failure, and are the focus of clinical trials. Indeed, assistance such as this in the otherwise reasonably compensated patient may even allow intrinsic myocardial recovery and reverse remodeling as has been shown for LVADs.[62-65]

Cardiac Transplantation

Historical Perspective

Orthotopic cardiac transplantation as it exists today is a highly successful procedure for the treatment of end-stage heart disease and is the result

of over 100 years of investigation and research.[66] The concept of transplanting solid organs dates back to the 19th century, but the necessary surgical techniques were not developed until the 1890s, with the work of Alexis Carrel, who perfected a vascular anastomosis technique that allowed heterotopic transplantation of kidneys into the necks of dogs.[67] He subsequently accomplished heterotopic transplantation of a canine heart where the organ was adequately perfused but nonfunctioning. These techniques were further developed by Mann and colleagues at the Mayo Clinic in the 1930s and led to the observation that autografts were usually successful, but that allografts seldom were, leading to the concept of rejection.[68] Pioneering work had also been done in Russia by Vladimir Demikhov since 1940. Demikhov was the first to successfully transplant a heart alone and a combined heart and lung orthotopically in an animal model. The techniques used were ahead of their time and included a novel technique for anastomosis of the recipient left atrium and pulmonary veins to the donor heart. Demikhov also implanted the first successful artificial heart into a canine model, which supported the animal for over 5 hours, although the device was too large for the chest to be closed.[10]

The modern era of human cardiac transplantation really started with Shumway's group at Stanford University throughout the 1950s and 1960s with development of cardiopulmonary bypass technology, and subsequently, demonstration of successful autotransplantation of the canine heart.[69] The surgical technique was perfected and remains largely unchanged today, termed the "Shumway technique," with preservation of the recipient left atrial posterior wall and pulmonary veins. By the mid 1960s, it was concluded by Shumway that the major barrier to successful mammalian cardiac allotransplantation was rejection.

At that time, the mechanisms of immune rejection were beginning to be elucidated. The first successful solid organ transplant in humans was a kidney transplant between identical twin infants in 1957. This led to continued experience with living related renal transplantation and development of early antirejection strategies, which at that time included total body irradiation and the first antirejection drug therapy with methotrexate, cyclophosphamide, and prednisone. These developments allowed the first human cardiac transplant by Barnard at Cape Town, South Africa, in 1967. Local irradiation, azathioprine, prednisone, and actinomycin C were used as immunosuppression. The patient survived 18 days but ultimately succumbed to *P. pneumoniae*.[70]

The landmark achievement of the first human orthotopic cardiac transplant prompted several further attempts in many centers over the

next year. In fact, 102 transplants were attempted worldwide over that time, all with poor outcomes. Much of this was due to surgical inexperience and lack of familiarity with immunosuppression and rejection. Most groups discontinued their efforts, but the Stanford group implemented criteria and protocols for detection of acute rejection early post transplant. Initially, this involved electrocardiographic, echocardiographic, and clinical parameters, but in 1973, the Stanford bioprome was developed and histologic criteria on endomyocardial biopsy were included and remain the mainstay of rejection surveillance. The discovery of cyclosporine A from a fungus in Swiss soil by Professor Jean-Francois Borel in 1976, and its subsequent introduction into clinical practice after successful animal studies,[71] was the breakthrough in the prevention of rejection, which allowed successful cardiac transplantation. The drug dosage and formulation were refined to minimize toxicity over the years. In the past 20 years, newer anti-T-cell agents such as tacrolimus (formerly FK-506) and sirolimus with less renal toxicity have become available.

Despite the great strides made in this field since the first transplant in 1967, the number of transplants performed worldwide has plateaued, primarily due to lack of donor organ supply.[72] This has instigated research and development in new and groundbreaking therapeutic avenues such as mechanical device therapy, which has ultimately led to the development of a totally implantable artificial heart, presently used as a bridge to transplantation. In the future, stem and progenitor cell therapy may have the potential to improve cardiac function in ischemic and dilated cardiomyopathy and thus reduce the demand for cardiac transplantation.

Demographics and Outcomes

The International Society for Heart and Lung Transplantation (ISHLT) has reported outcome data on transplant recipients annually for the past 25 years. The most recent data are summarized below.[73]

Demographics. The number of patients transplanted since the previous report of the ISHLT in 2006 showed evidence of the first increase in 13 years. The primary indication for cardiac transplantation has shifted in the past 5 years toward a slight predominance of patients with nonischemic cardiomyopathy (50%) vs ischemic (34%) for January to June 2007. Overall, the relative contribution of patients with ischemic cardiomyopathy has actually declined over the past 10 years. The remaining indications represent a minority of patients with valvular (2%) and congenital heart disease (3%) and those retransplanted (2%). An increas-
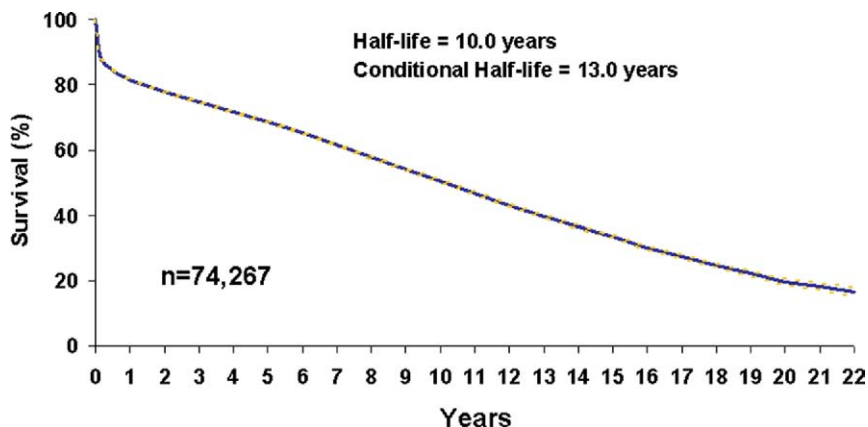
FIG 6. Kaplan-Meier survival for all cardiac transplants (1/1982-6/2006). (Color version of figure is available online.)

ing number of patients are now on inotropic (41%) or mechanical support (including LVADs, 29%) at the time of cardiac transplantation.

The age of both donors and recipients has increased in the past 20 years. Almost 25% of cardiac transplant recipients in the previous year were over the age of 60 years, with a relative fall in numbers of recipients aged 40-49 years.[72] Donors over the age of 50 years, virtually unheard of 20 years ago, now comprise >12% of donors worldwide. A geographic difference also exists in mean donor age, with donors in Europe being significantly older than in the USA. Twenty percent of European donors are over 50 years old, whereas in the USA that figure is closer to 10%.

Outcomes. Since the ISHLT started reporting outcomes on transplanted patients in 1982, early survival (up to 1 year) post transplantation has improved steadily.[74] However, long-term mortality has not changed and in fact the overall survival patterns remain largely unchanged with a steep fall in survival up to 6 months and a linear decrement in survival thereafter, at approximately 3.5% per year. The current transplant half-life is 10 years worldwide for adult and pediatric cardiac transplant recipients combined, with a half-life of 13 years for those surviving the first year. This represents a steady improvement over the past 20+ years due to the improvements in early survival (Fig 6). In particular, survival for patients retransplanted has improved and, based on data on patients undergoing repeat cardiac transplantation between 2002 and 2006, is currently similar to those transplanted for the first time (approximately 85% 1-year survival in those surviving the first year).[73]

TABLE 2. Risk factors for mortality within 1 year for transplants performed January 2002 through June 2006 (n = 8823)

Variable	n	Relative risk	P value	95% Confidence interval
Temporary circulatory support[a]	137	3.19	<0.0001	2.32-4.37
Diagnosis: congenital vs cardiomyopathy	228	1.89	0.0002	1.35-2.64
Recipient on ventilator at time of transplant	248	1.50	0.0044	1.13-1.98
Recipient history of dialysis	273	1.48	0.0021	1.15-1.91
Recipient with infection requiring intravenous drug therapy within 2 wks before transplant	923	1.30	0.0047	1.08-1.56
Long-term pulsatile device	1456	1.26	0.0205	1.04-1.53
Not ABO-identical	1288	1.25	0.0067	1.06-1.46
Prior transfusion	1749	1.19	0.0432	1.01-1.41
Diagnosis: coronary artery disease vs cardiomyopathy	3939	1.16	0.0431	1.00-1.35
Recipient on inotropes at time of transplant	3673	0.85	0.0282	0.73-0.98
Recipient age (J-shaped)			<0.0001	
Recipient height (inverse linear)			<0.0001	
Donor age (curvilinear)			<0.0001	
Donor BMI (inverse linear)			0.0288	
Transplant center volume (inverse linear)			0.0032	
Ischemia time (linear)			0.0060	
Pulmonary artery diastolic pressure (linear)			0.0004	
Serum bilirubin (linear)			0.0006	
Serum creatinine (linear)			0.0001	

[a]Including ECMO and Abiomed.

The risk factors for death within 1 year and, in those surviving the first year, for death within 5 years post cardiac transplantation are shown in Table 2. In the current era, the most significant risk factors for death post cardiac transplantation in the first year remain the requirement for short-term extracorporeal mechanical support post transplantation, and congenital heart disease as an indication for transplantation. After the first year, the highest risk factors for death within the first 5 years are ventilator dependence at the time of transplant, the development of cardiac allograft vasculopathy within the first year, and a diagnosis other than cardiomyopathy, coronary artery disease, or valvular heart disease before transplantation.

The commonest causes of death up to 30 days, in the first year and up to 5 years, are shown in Table 3. Graft failure remains the commonest cause of death within 30 days and includes ischemic/reperfusion injury, right heart failure, and acute rejection. Beyond 30 days, infection becomes prominent as the commonest cause of death up to the first year as the cause of 33% of deaths post cardiac transplantation within that

TABLE 3. Risk factors for mortality within 5 years conditional on survival to 1 year ($n = 4144$)[a]

Variable	n	Relative risk	P value	95% Confidence interval
Ventilator at time of transplant	86	2.00	0.0023	1.28-3.13
Cardiac allograft vasculopathy within first year	210	1.94	<0.0001	1.45-2.58
Diagnosis: other[b] vs cardiomyopathy	112	1.79	0.008	1.16-2.75
Rejection between discharge and first year	1415	1.39	0.0002	1.17-1.65
Recipient history of diabetes	779	1.38	0.0016	1.13-1.69
Drug-treated rejection before discharge	732	1.35	0.0038	1.10-1.65
Other surgical procedures (excluding cardiac reoperation) before discharge	457	1.30	0.0394	1.01-1.66
Diagnosis: coronary artery disease vs cardiomyopathy	1986	1.28	0.0122	1.06-1.55
Drug-treated infection before discharge	884	1.21	0.0624	0.99-1.47
Recipient age (U-shaped)			<0.0001	
Donor age (linear)			0.0006	
Pulmonary vascular resistance (linear)			0.0057	
Donor body mass index (linear)			0.0062	
Donor/recipient weight ratio (inverse)			0.0106	

[a]Includes transplants performed January 2000 through June 2002.
[b]All pretransplant diagnoses except cardiomyopathy.

TABLE 4. Leading causes of death post cardiac transplantation

Up to 30 days	Proportion of all deaths
Up to 30 days	
Graft failure	40%
Multi-organ failure	14%
Infection	13%
31 days to 1 year	
Infection[a]	33%
Graft failure	18%
Acute rejection	12%
5 years	
Cardiac allograft vasculopathy	30%
Malignancy	22%
Infection[a]	10%

[a]Excluding CMV infection.

period (Table 4). After this time point, cardiac allograft vasculopathy is the most frequent cause of death, representing 33% of all deaths within 5 years post cardiac transplantation, closely followed by malignancy (23% of deaths).

Transplant Recipient Selection

The current American College of Cardiology/American Heart Association guidelines on selection of adult patients for cardiac transplantation

TABLE 5. Cardiac transplantation—indications and contraindications

Absolute indications
  Hemodynamic compromise secondary to HF
    —Refractory cardiogenic shock
    —Dependence on IV inotropic support for adequate organ perfusion
    —Peak VO_2 <10 mL/kg/min
  Severely limiting non-revascularizable ischemic heart disease affecting daily living
  Recurrent symptomatic VT refractory to therapy
Relative indications
  Peak VO_2 11-14 mL/kg/min with significant limitation of functional capacity
  Recurrent unstable angina refractory to current therapy
  Recurrently labile fluid balance/renal function in chronic heart failure despite full patient
    compliance with therapy
Insufficient indications
  Presence of the following without other indications for transplantation:
    —Impaired LV systolic function
    —Previous history of class III-IV heart failure
    —Peak VO_2 >15 mL/kg/min
Contraindications
  Age
  Coexistent systemic illness
  Irreversible pulmonary hypertension
  Parenchymal lung disease
  Acute pulmonary embolus
  Severe peripheral vascular disease
  Irreversible renal and hepatic dysfunction
  Diabetes with severe end organ damage
  Severe obesity
  Severe osteoporosis
  Active infection
  Psychosocial issues
  Drug addiction, including nicotine

are set out in their practice guidelines for the management of chronic heart failure in the adult.[75] The primary focus is in patients with severe functional impairment and/or dependence on inotropic support. Rarely, recurrent malignant arrhythmias refractory to medical therapy and debilitating refractory angina pectoris secondary to severe non-revascularizable ischemic heart disease may be indications. Contraindications to cardiac transplantation are all relative and dependent on how modifiable they are before surgery. They include pulmonary disease, pulmonary hypertension, diabetes with complications, systemic disease (including malignancy), and peripheral vascular disease. Age is also included, but this is an area of controversy as data regarding outcomes in older recipients have been conflicting.[76,77] The indications for and contraindications to cardiac transplantation are summarized in Table 5.

Transplant Donor Selection

Selection of a potential donor requires several criteria to be met. First, national or regional criteria for brain death must be met. The electrocardiogram and the echocardiogram should be normal. If a donor older than 45 years is being considered (often for an older recipient), coronary angiography is usually performed to exclude significant coronary artery disease. Otherwise, the risk factor profile for coronary artery disease should be low and there should be no evidence of untreated acute infection or systemic malignancy. The human immunodeficiency virus and hepatitis screens should be checked and confirmed negative. Potential donors with cardiac trauma are usually excluded.

The matching of a suitable donor to a recipient is dependent on a limited number of key issues, as follows.

1. Blood type. ABO matching is mandatory. Matching of rhesus status is not required.
2. Body size. Generally, the donor should be at least 80% of the body weight of the recipient.
3. Pulmonary vascular resistance. Where this is high (generally more than 4-5 Wood Units) in the recipient, a larger donor heart is usually selected to ensure adequate RV functional reserve. In addition to pulmonary vascular resistance, the pulmonary artery pressure is also considered, and in particular, the assessment of reversibility of high pulmonary pressures seen in some patients with chronic heart failure.
4. Recipient stability. Where the recipient is unstable (status 1 vs status 2), the urgency of finding a suitable donor heart occasionally requires some compromise on an "ideal" match as outlined above.
5. Geographic location of donor. This always needs to be considered to ensure the lowest possible cold-ischemic time of the heart after it has been explanted from the donor. Once this rises beyond 4 hours, outcomes may be compromised. This is accentuated if there is significant hypertrophy of the donor organ.
6. Anti-HLA antibody titer. Due to the short time window of permitted cold-ischemic time in the setting of heart transplantation, unlike renal transplants, HLA cross-matching is only performed if titer of preformed antibodies in the recipient ("panel-reactive antibodies" or PRA level) is significant. This titer of preformed antibodies in the recipient is part of the routine pretransplant assessment of the recipient and reflects the degree of sensitization of the patient to foreign antigens of HLA A, B, and DR subtype. This is performed by incubating recipient serum in different wells with a random panel of donor lymphocytes.

The result is represented as a percentage of total wells on a panel, which show evidence of a positive reaction, hence the term PRA.[78] However, numerous variations in methodology exist and most recently they have included flow cytometric virtual cross-match.[79] However, there is also variation in the interpretation of results—most programs consider a titer greater than 10% to be significant. However, some institutions have considered any elevation or only titers greater than 20%-25% to be of significance.[80]

The importance of the pretransplant PRA level has been known for some time, and elevated PRA titres have been associated with increased risk of hyperacute rejection, antibody and cell-mediated rejection, and cardiac allograft vasculopathy.[81-83] As a result, patients with significantly elevated pretransplant PRA levels (>10% according to the American Society of Histocompatibility and Immunogenetics and United Network for Organ Sharing) require HLA cross-matching to a donor organ.[84,85]

Operative Details

The original operative technique described by Shumway and coworkers involved removal of the native heart and anastomosis of the recipient heart at midatrial level bilaterally[86] (Fig 7A). This biatrial anastomosis technique was shown to increase the incidence of atrial arrhythmia, right atrial thrombus, and tricuspid valve dysfunction.[87,88] In the late 1980s, a new technique was described that preserved the entire donor heart intact but involved 8 anastomoses—the 4 pulmonary veins, the superior and inferior venae cavae, the pulmonary artery, and the aorta. This so-called "total transplantation technique" was pioneered by Yacoub's group in 1989 at the Harefield Hospital, [89-91] but was first described by Carpentier's group in 1991.[92] The disadvantage of this technique was the increased time required for anastomosis of the pulmonary veins and significantly increased cold-ischemia time of the donor heart. Therefore, the procedure was simplified in 1991 with preservation of the recipient pulmonary veins and anastomosis of a small cuff of recipient left atrial tissue to the donor left atrium, but retaining the anastomosis of the venae cavae and thus sparing integrity of the donor right atrium.[93] This "bicaval technique" has been reported to preserve atrial contractility, sinus node function, and tricuspid valve competence but also increases the operative time, including the duration of cold ischemia[94] (Fig 7B). Recent evidence has again shown short-term clinical benefits of the bicaval technique when compared with the biatrial technique, but there is insufficient evidence to date on long-term outcomes.[94]
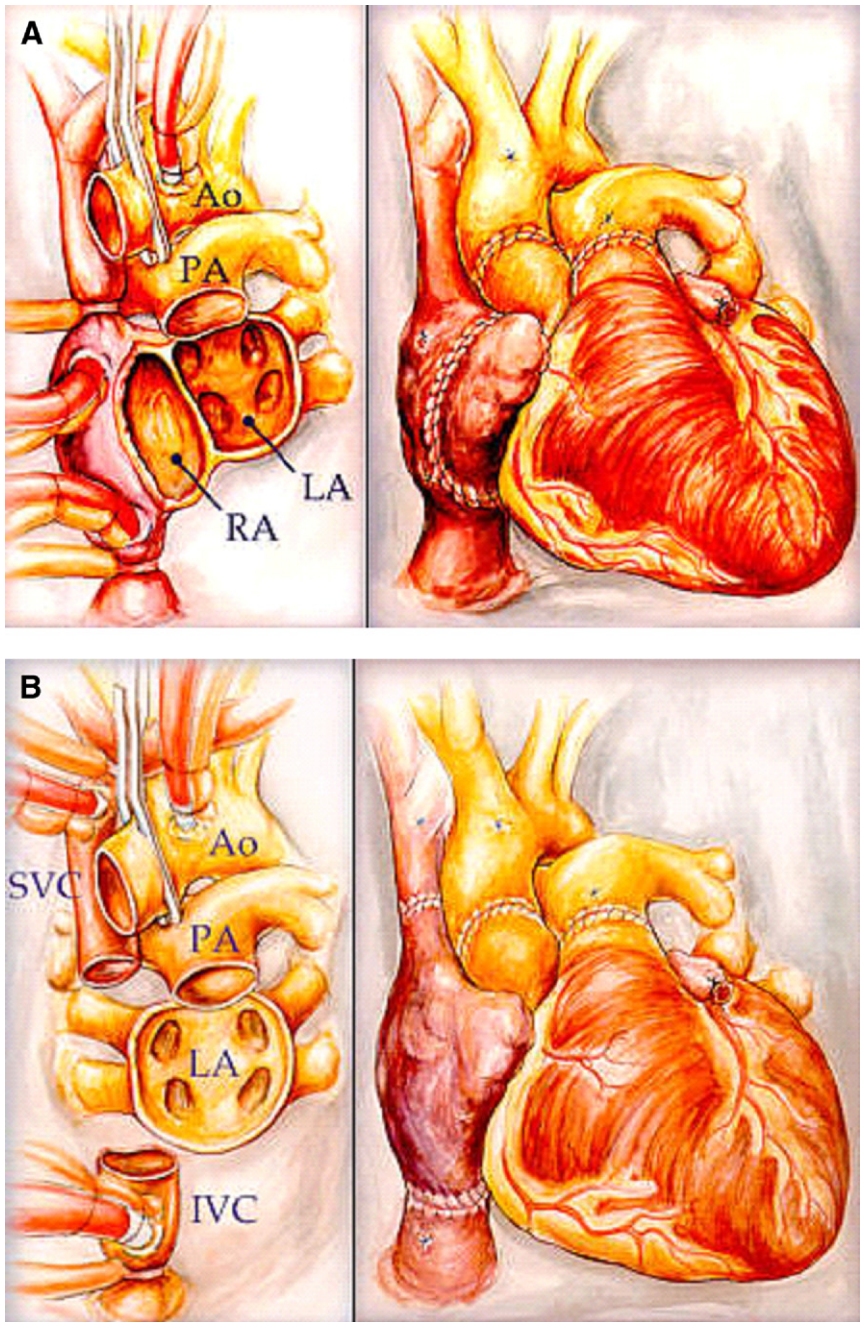
FIG 7. Standard Shumway anastomosis (A) and bicaval anastomosis (B). (Reprinted with permission from Mavroudis C, Backer CL. Pediatric Cardiac Surgery, Third Edition, Chapter 42. Philadelphia: Mosby, 2003:744-45.) (Color version of figure is available online.)

Medical Issues Post Cardiac Transplantation

Immunosuppression. In practical terms, this can still be viewed in initial induction strategies and chronic immunosuppression regimens. Induction therapy traditionally used the anti-T-cell receptor monoclonal antibody OKT3. However, use of this agent was in less than 3% of cardiac transplants performed in 2007. The use of anti-thymocyte globulin has remained stable at approximately 20%.[73] The rationale for induction therapy is to reduce the risk of early acute rejection through enhanced immunosuppression, and in addition, the risk of postoperative renal dysfunction through a delay in commencement of calcineurin inhibitor therapy.[95] However, induction therapy is not without risk, and substantive evidence has linked it to an elevated risk of development of posttransplant lymphoproliferative disorder.[96,97] Therefore, the use of induction therapy varies among centers worldwide and almost half elect to avoid its use completely. A recent retrospective study of data compiled in the cardiac transplant research database investigated the effect of no induction therapy, or induction therapy with OKT3 or anti-thymocyte globulin preparations on outcomes.[98] Induction therapy had a positive effect on survival only in patients at highest risk of rejection death—otherwise the effect was negative and survival was poorer.[98] The authors concluded therefore that the patient groups most likely to benefit from induction therapy are non-black patients under 35 years who have been supported by a LVAD for greater than 6 months and with a high PRA, or black patients under 40 years with the same risk factors, and under 25 years with just an elevated PRA. In addition, a recent retrospective review of over 3000 cardiac transplant recipients in Spain has shown that the concomitant use of antiviral strategies negates the increased risk of lymphoma conferred by use of anti-thymocyte globulin or OKT3.[99]

The newer interleukin-2 antagonists are under evaluation. Evidence to date has suggested better tolerability with basiliximab compared with OKT3, but no significant difference in outcomes.[100] Where basiliximab and dacluzimab have been studied in randomized controlled clinical trials compared with placebo, no significant difference in time to first acute rejection was seen for basiliximab,[101] but a 12% decrease in absolute risk of moderate or severe cellular rejection was seem for dacluzimab.[102] However, a concerning increase in the number of deaths at 1 year was seen in the dacluzimab group compared with placebo, which was attributable to increased risk of life-threatening infection.[102] The role of IL-2 antagonists in induction therapy is still under evaluation.

Maintenance immunosuppression varies among centers. The traditional model of a calcineurin inhibitor (cyclosporine or tacrolimus), an antiproliferative agent (azathioprine or Mycophenolate), and a steroid is usual, but use of tacrolimus in preference to cyclosporine has increased in recent years and is now the most common calcineurin inhibitor in use on a worldwide basis.[73] Two randomized clinical trials have studied tacrolimus in direct comparison with cyclosporine. A European-based multicenter study on over 300 patients showed a significantly lower incidence of severe rejection in the tacrolimus-treated patients at 6 months but no difference in patient or graft survival at 18 months.[103] A smaller study from the USA where patients did not receive induction therapy showed no difference in survival or incidence of severe rejection between groups but a significantly lower incidence of renal dysfunction and hypertriglyceridemia in the tacrolimus-treated patients.[104] In addition, a nonsignificant trend was observed toward a lower requirement for antihypertensive therapy in the tacrolimus group.

Mycophenolate has replaced azathioprine as the antiproliferative agent of choice and is currently used in over 70% of transplanted patients at 1 year. The advantages of mycophenolate over azathioprine post cardiac transplantation include a reduced incidence of acute rejection and mortality, and possibly even a reduced incidence of cardiac allograft vasculopathy.[105-108] The underlying mechanisms for this benefit may include preferential anti-B-cell activity compared with azathioprine and reduced production of anti-HLA antibodies post transplantation.[109,110]

A recent study that compared the cyclosporine/mycophenolate/prednisone, tacrolimus/mycophenolate/prednisone, and tacrolimus/sirolimus/prednisone combinations showed a significantly lower incidence of grade >2R or hemodynamically significant rejection at 1 year in the 2 tacrolimus-based therapy groups compared with cyclosporine-based therapy.[111] The tacrolimus/mycophenolate/cyclosporine combination resulted in the most optimal preservation of renal function and the lowest triglyceride levels. Tacrolimus as monotherapy is also being analyzed prospectively in the TIC-TAC trial (Tacrolimus In Combination, Tacrolimus Alone, Compared).[112]

In terms of combination of these agents with induction therapy, the combination of the tacrolimus/mycophenolate/cyclosporine combination and IL-2 antagonist resulted in a lower incidence of early infection than cyclosporine/prednisone in combination with either azathioprine or mycophenolate and OKT3 induction therapy.[113]

Newer agents such as the mammalian target of rapamycin (mTOR) inhibitor rapamycin (sirolimus and its derivative everolimus, otherwise known as proliferation signal inhibitors) are becoming more common,

made popular by its potent immunosuppressive capacity coupled with cytostatic effects outside the immune system.[114-116] While the evidence that proliferation signal inhibitors used in combination with calcineurin inhibitors may reduce the incidence of cardiac allograft vasculopathy (CAV), questions were raised regarding the increased renal toxicity (thought to be due to potentiation of the nephrotoxic effect of calcineurin inhibitors by sirolimus) and more frequent hypertension.[117,118] The first evidence of using sirolimus for primary immunosuppression after heart transplantation demonstrated that complete and slow calcineurin inhibitor withdrawal and replacement with sirolimus (leaving secondary immuno-suppressive agent unchanged) can be achieved safely[119,120] and may have long-term benefit effects. In a subsequent study, sirolimus as a primary immunosuppressive agent was found to attenuate the progression of CAV by reducing intimal hyperplasia as evidenced by 3D intravascular ultrasonography (IVUS). Treatment with azathioprine or mycophenolate mofetil did not significantly affect the results; there was no difference in late rejection episodes.[121] In addition proliferation signal inhibitors may have other beneficial therapeutic effects in heart transplant recipients, including regression of cardiac hypertrophy with consequent improve-ment in cardiac allograft function.[122,123]

Use of everolimus in combination with full-dose cyclosporine in de novo cardiac transplant recipients reduced the risk of cytomegalovirus (CMV) infection by almost one-third and decreased the severity of the disease compared with azathioprine-based therapy.[124-126] These data also confirmed meta-analysis in de novo renal transplant recipients, which showed that the use of mTOR inhibitor with a calcineurin inhibitor and corticosteroids was associated with a significant, 51% reduction in the rate of CMV infection compared with antimetabolites.[127]

The advantages in renal function have been demonstrated in several studies.[119,121] Other long-term medical benefits from calcineurin inhibitor (CNI) withdrawal include improvements in hypertension, hyperuricemia, hyperkalemia, edema, hypomagnesemia, and dyspnea. Furthermore, there is evidence of improved quality of life after calcineurin inhibitor withdrawal.[119,120,128,129]

A calcineurin inhibitor-free regimen was more effective when initiated within the first 2 years following transplantation,[121] but the results could not be projected to the implementation of sirolimus as a primary immunosuppressant in the immediate post transplant period because of concerns regarding sirolimus and wound healing. Although no wound-healing problems were reported in the everolimus study, de novo use of

sirolimus was associated with a greater incidence of impaired wound healing than other immunosuppressive agents.[125,130-133]

Complications Post Cardiac Transplantation. **Early Complications.** Early complications after cardiac transplantation include primary graft failure, acute and hyperacute rejection, arrhythmia, bleeding, and infection.

Primary graft failure includes ischemic/reperfusion injury and right heart failure secondary to pulmonary hypertension. It still accounts for up to 40% of deaths within the first 30 days post cardiac transplantation.[73] Extended cold-ischemic time of the donor heart and elevated pulmonary vascular resistance in the recipient pretransplantation are significant risk factors. Treatment usually requires inotropic support, use of vasodilators to reduce pulmonary and systemic afterload, and occasionally mechanical support. In rare circumstances emergent retransplantation is required.

Hyperacute rejection is nowadays a rare form of early rejection, which is seen as soon as the donor heart is initially perfused with blood from the recipient. This is due to preformed donor-specific antibodies in the recipient circulating within the coronary circulation of the donor heart and severe microvascular injury and thrombosis, frequently resulting in loss of the graft. It is associated with a high titer of preformed antibodies (PRA) in the recipient, which is usually detected on screening in the pretransplant phase. Patients who fall into this category usually have prolonged waiting times for a suitable organ as they require extensive cross-matching of a potential donor heart to minimize the chances of this rare but devastating complication occurring. This process has resulted in hyperacute rejection being very rarely encountered in modern practice.

Acute rejection is common and usually T-cell-mediated (cellular) but sometimes is due to recipient antibodies to donor antigens (humoral). Interestingly, the most recent ISHLT analysis has shown that current practices with induction therapy impact little on this problem. In fact, patients treated with OKT3 induction therapy had more acute rejection episodes in the first year post transplant than patients treated with other forms of induction therapy (ie, anti-thymocyte globulin or anti-IL-2 antibodies) or no induction therapy at all.[73] It has also been shown that patients treated with tacrolimus in preference to cyclosporine early post transplant have fewer rejection episodes in the first year, especially if they were treated in combination with mycophenolate.[103]

Acute rejection is not usually symptomatic unless fulminant and severe, but its detection is important as frequency of episodes correlates with reduced graft survival (Fig 8) and possibly also with the incidence of cardiac allograft vasculopathy.[134,135] Therefore, screening is required
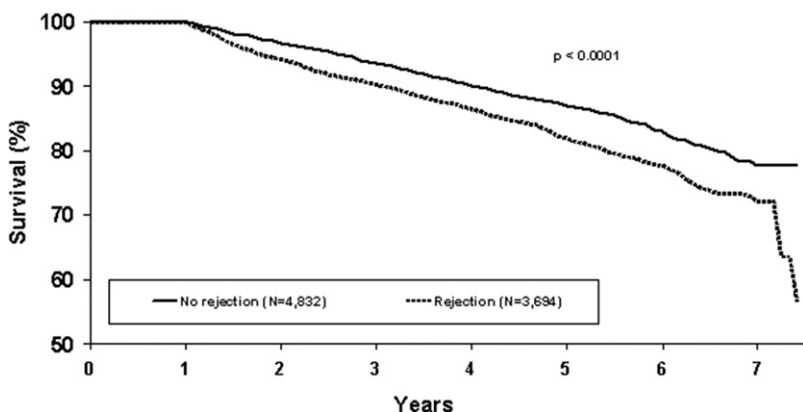
FIG 8. Survival post cardiac transplantation for adult recipients by incidence of rejection at one year (ISHLT data 2007).

with frequent endomyocardial biopsy. Usually, this is performed weekly for the first month and then every 2 weeks until 3 months post transplant. After this, biopsies become less frequent. Alternative approaches are under investigation to reduce the number of biopsies that need to be performed as the endomyocardial biopsy procedure itself has been associated with increased risk of tricuspid valve injury over time. These include the use of microarrays for identification of key (candidate) genes upregulated and downregulated in early rejection. Data have already been shown that confirms the utility of detection of these genetic markers to rule out significant cardiac rejection, which may potentially have a significant impact in reducing the burden of endomyocardial biopsy on cardiac transplant recipients.[136,137] Studies are underway that are evaluating the utility of this mode of testing for longitudinal analysis of patients in their rejection profile.[138]

The ISHLT grading system for *acute cellular rejection* was changed in 2004. Currently, the following system is used (Fig 9):

Grade 0—no rejection (Fig 2A)

Grade 1 R, mild—interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage (Fig 2B)

Grade 2 R, moderate—2 or more foci of infiltrate with associated myocyte damage (Fig 2C)

Grade 3 R, severe—diffuse infiltrate with multifocal myocyte damage, with or without edema, hemorrhage, or vasculitis (Fig 2D)

Thus, grade 1 R includes grades 1 A, 1 B, and 2 in the 1990 system; grade 2 R was grade 3 A; and grade 3 R was grades 3 B and 4.
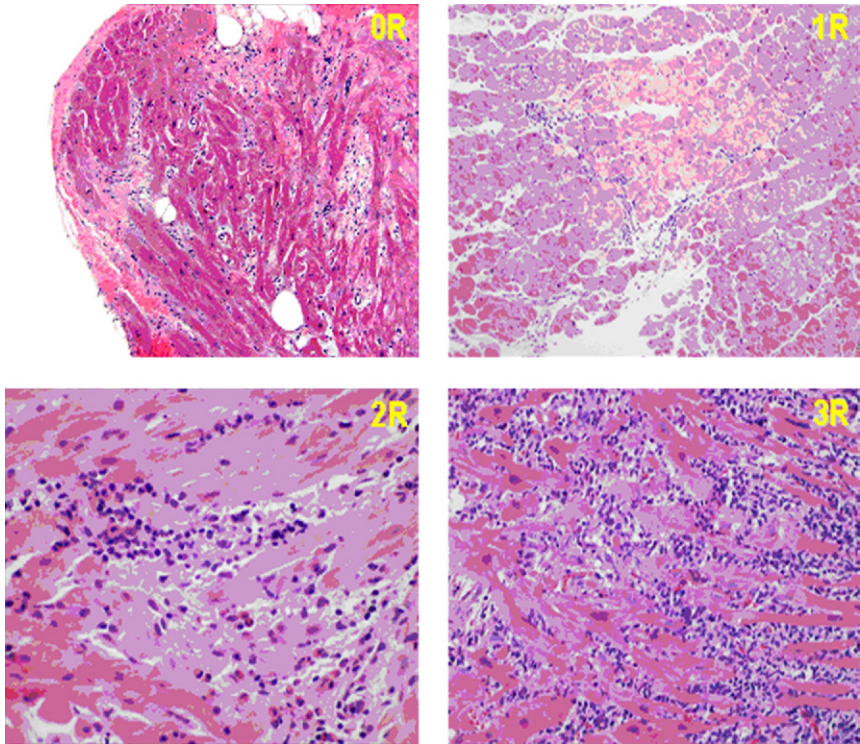
FIG 9. Cell-mediated rejection—2004 ISHLT grading. (Color version of figure is available online.)

Humoral or *antibody-mediated rejection (AMR)* (Fig 10) is a less well-recognized entity in cardiac transplantation medicine and is probably underdiagnosed. However, it is associated with an increased incidence of cardiac allograft vasculopathy and mortality.[134,139] Histologically, it is characterized by endothelial swelling and the presence of macrophages and neutrophils in the capillaries with fibrin deposition.[140] The immuno-fluorescence markers used for diagnosis of AMR have changed repeatedly over the years as previously they have failed to correlate with the clinical severity of the condition. Currently, the ISHLT guidelines recommend staining for complement C3d and C4d deposition and for CD68-positive macrophages within and on the capillaries (Fig 5). Analysis of patient serum for the presence of anti-HLA I and II antibodies is also recommended.[141] One recent series has shown that generally AMR is seen most commonly early in post cardiac transplantation and in these cases association with elevated antidonor HLA antibodies is frequent.[142]
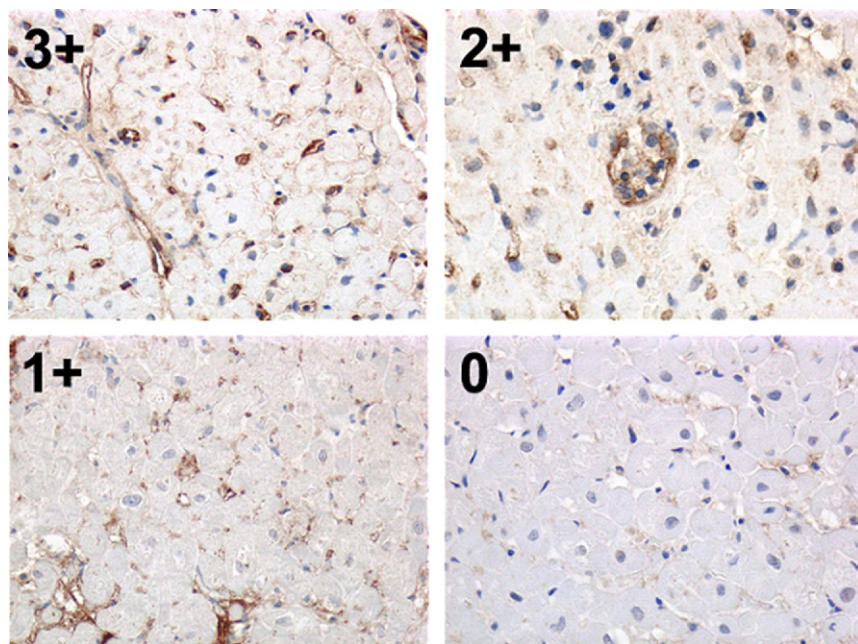
FIG 10. Antibody-mediated rejection with intensity of C4d staining, 0-3+. (Image courtesy of Dr. D. Miller, Mayo Clinic.) (Color version of figure is available online.)

However, this is less common in patients developing AMR later in their post-transplant course, where, instead, it is associated with malignancy or recent infection, suggesting activation of antibody-mediated immunity by a new antigen present on an invading pathogen or expressed on tumor cells.[143]

Arrhythmia post cardiac transplantation is common. Frequently, patients are tachycardic due to denervation of the donor heart. Occasionally, atrial fibrillation occurs, as a common complication of all cardiac surgery. In transplant patients, bradycardia and junctional rhythms are not unusual, particularly when the cold-ischemic time of the donor heart has been prolonged and ischemic sinus and atrioventricular nodal injury has taken place.[87] Most arrhythmia post cardiac transplantation relates to sinus node dysfunction, which is caused mainly by cold ischemia. Sinus node function generally improves with time, but occasionally (4%-12% of cases), permanent pacemaker implantation is required before discharging the patient from hospital, and 1 study has suggested that dual chamber atrioventricular sequential pacing is preferable in this respect.[144]

TABLE 6. Risk factors for development of CAV after 5 years for transplants performed April 1994 through June 2002 (n = 3610)

Variable	n	Relative risk	P value	95% Confidence interval
Diagnosis: congenital vs cardiomyopathy	52	1.77	0.0434	1.02-3.10
Diagnosis: coronary artery disease vs cardiomyopathy	1703	1.23	0.0289	1.02-1.48
Other surgical procedures (excluding cardiac reoperation) before transplant discharge	282	0.66	0.027	0.46-0.95
Transplant year: 2000 vs 2001/02	472	0.50	0.0084	0.30-0.84
Recipient history of diabetes before transplant	505	1.24	0.0691	0.98-1.57
Recipient age (inverse linear)			0.0052	
Donor age (linear)			<0.0001	
Donor age by donor gender interaction			<0.0001	
Transplant center volume (linear)			0.067	

Late Complications. CAV is the leading cause of late morbidity and mortality in heart transplant recipients (Table 6).[145] Angiographic studies indicate that CAV occurs in 42% of all heart transplant patients[146] and IVUS, a more sensitive technique, detects CAV in 75% of patients by 3 years after transplantation.[147] The ISHLT registry in 2007 indicates that 5 years after cardiac transplantation CAV and late graft failure (likely due to CAV) together account for 30% of deaths and over 50% of adult recipients will have angiographic evidence of CAV at 10 years (Fig 11).[72,148]

The pathophysiology of CAV is thought to be multifactorial, involving several immunologic and nonimmunological factors. In addition to well-known risk factors such as hypertension, younger recipient age, male gender, and pre-existing donor coronary artery disease, it has been shown that markers of metabolic syndrome are associated with increased incidence of CAV and worse prognosis after heart transplantation.[149] Although CAV may develop at any stage after transplantation, events during the first year appear to be important in its pathogenesis[150] and risk factors in the donor may also play a role.[151]

The diffuse nature of CAV suggests an immune etiology.[152,153] Experimental evidence has shown that immune activation may lead to an inflammatory process in the vascular endothelium resulting in tissue destruction and potentiation of CAV.[151,154-160] HLA-DR mismatch between donor and recipient are also a risk factor; however, HLA-B mismatch may be protective.[161] The importance of systemic inflammation in CAV has been shown in several studies.[162-165]
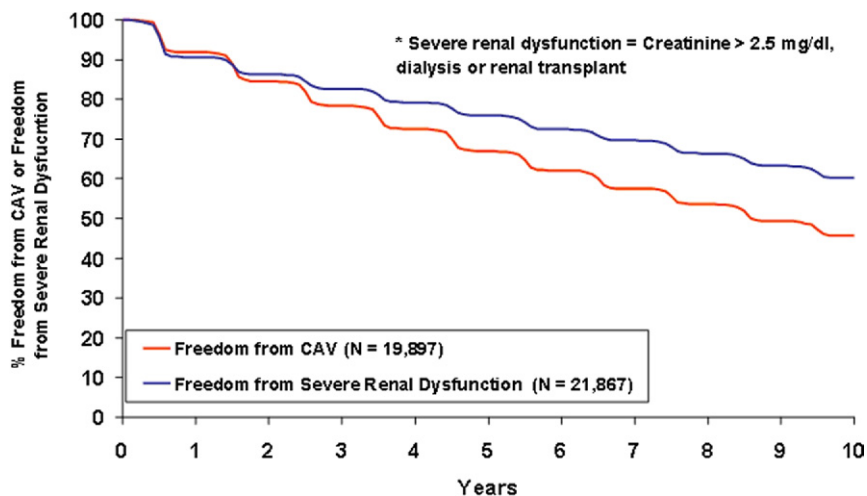
FIG 11. Freedom from cardiac allograft vasculopathy and from severe renal dysfunction (follow-ups: April 1994-June 2007). (Color version of figure is available online.)

Endothelial dysfunction is an early feature of cardiovascular disease,[166] contributes to the pathogenesis of CAV, and is associated with an increase in the risk of cardiovascular events.[167-169] Cyclosporin, the mainstay of immunosuppression, is thought to impair endothelial function[170,171] by increasing endothelin levels,[172] impairing synthesis of nitric oxide and the generation of free radicals.[173,174]

The role of CMV infection is controversial—evidence dates back almost 20 years showing an association with CAV.[175-178] However, recent evidence has cast some doubt on this association.[179,180]

CAV is a diffuse process affecting large epicardial vessels and the microcirculation and may also involve the coronary veins of the transplanted heart. Histologically, CAV is characterized by concentric fibrous intimal hyperplasia, smooth-muscle proliferation, and inflammation and is accompanied by fibrous replacement of the media,[181] impaired positive vascular remodeling[182]—all these factors contribute to progressive luminal narrowing,[183,184] reduction of myocardial blood flow,[185] and endothelial dysfunction.[168]

The diagnosis of CAV has traditionally employed coronary angiography, which has a high specificity of 97.8% but only moderate sensitivity of 79.3% in long-term follow-up.[186] The intimal changes in CAV are best detected by intravascular ultrasound, which is the gold standard for the early diagnosis of CAV[147,187-189] and allows detection of the changes in atherosclerotic burden with more accurate evaluation of interventions

aimed at preventing or retarding coronary artery disease.[147,190] IVUS, however, is also limited in the diagnosis of CAV, imaging only the larger epicardial arteries and not the smaller vessels and branches. A growing body of evidence has demonstrated that virtual histology VH-IVUS is a reliable tool and offers an in vivo method to characterize different types of plaque morphology (eg, fibrous, fibrofatty, dense calcium, and necrotic core).[191-193] It was recently suggested that simultaneous assessment of "virtual histology" with IVUS may be a useful tool in studying the mechanism and the predicting the progression of CAV.[194]

Allograft vasculopathy is a phenomenon not limited to cardiac transplantation: a similar process also limits long-term graft survival in other solid organ transplants.[195-197]

Although there is evidence of some reinnervation of cardiac allografts, most transplant recipients do not experience anginal pain with myocardial ischemia or infarction. Therefore, the commonest presentation of CAV is silent myocardial infarction, congestive cardiac failure, or arrhythmia, which may present as sudden cardiac death.[198,199] Once established, CAV is generally irreversible, and because of its diffuse rather than localized nature, angioplasty or aortocoronary bypass provides limited long-term benefit, although either may have a role in the treatment of localized lesions.[200,201] Modification of traditional risk factors may attenuate disease progression and improve outcome.[202-206] There is growing evidence for the role of statins in the prevention of CAV in animal models[207] and in humans.[165,208-210] Additional benefits of statins may include prevention of progression of post transplant renal dysfunction.[211] In severe CAV, however, the prognosis is grave and the only treatment option is retransplantation.

Progress in understanding the pathogenesis and natural history of CAV during the past years and advantages in diagnosis, however, have paved the way for new therapeutic approaches. There is recent evidence that the use of mTOR inhibitors such as sirolimus (rapamycin) and everolimus, a synthetic derivative, may attenuate the progression of CAV.[125,132,212-214] Sirolimus was shown to be less deleterious to the vasculature than cyclosporin, maintaining nitric oxide homeostasis and reducing the plasma endothelin levels.[68] Sirolimus-based immunosuppression results in less pronounced coronary epicardial endothelial dysfunction compared with immunosuppression with cyclosporin. In addition, sirolimus treatment was associated with preserved endothelium-independent function. Moreover, the lower systemic blood pressure in the sirolimus group suggests that the beneficial vascular effects of sirolimus may extend beyond the coronary circulation.[215]

Chronic kidney disease after cardiac transplantation is a major source of morbidity and mortality.[216,217] Analysis of data from 1994 to 2006 has shown that the incidence of renal insufficiency in cardiac transplant recipients has been increasing—at 10 years post cardiac transplant 98% of patients have hypertension, and 14% of patients have renal insufficiency (Fig 11). The degree of renal dysfunction following cardiac transplantation ranges from moderate renal impairment to chronic dialysis and renal transplantation (8% heart transplant recipients with creatinine > 2.5 mg/dL and 5% on hemodialysis, Fig 6).[148] The increasing incidence of renal dysfunction post transplant may reflect the fact that cardiac transplantation is being offered to "higher risk" patients with more pre-existing renal insufficiency.

Many of the conditions that lead to severe heart failure (hypertension, atherosclerosis, diabetes) also result in intrinsic renal disease; however, calcineurin inhibitor use results in progressive damage of the kidneys mediated through several mechanisms. Many changes are considered irreversible. While the cyclosporine A-sirolimus combination worsens renal function by exacerbating and potentiating cyclosporine-mediated nephrotoxic damage,[117,118] kidney function significantly improved after calcineurin inhibitors were completely stopped and replaced by mycophenolate mofetil and sirolimus.[119,120,129,218]

Infection with both usual community-acquired and opportunistic pathogens is increased in patients on chronic immunosuppression. The risk of infection for any individual cardiac transplant recipient depends on the epidemiologic exposures of any individual and also the net status of immunosuppression. The epidemiologic exposure for each patient is variable and dependent on geographic location, occupation, leisure pursuits, and exposure to animals and young children. This is carefully ascertained during the transplant workup to ensure appropriate precautions and antibiotic prophylaxis, where necessary, are taken by the future recipient. This is also critically important when the patient presents with infection post transplantation, to ensure a timely and accurate diagnosis is made, as untreated infection in the immunocompromised frequently progresses rapidly.

The immunosuppression requirements of the recipient changes over time—it is highest immediately after transplantation when induction therapy is frequently used. This also coincides with the highest incidence of post transplantation infection, which remains high for the first 6 months after transplant. With increasing time following transplantation, in the absence of significant rejection, steroid therapy is tapered and often

discontinued, and other maintenance immunosuppressive agents are reduced. This usually results in a reduced risk of infection. However, where significant rejection occurs and immunosuppression is increased, so too does the infection risk.

Common pathogens include community-acquired pathogens such as common respiratory viruses (eg, influenza, parainfluenza, respiratory syncytiovirus, and adenovirus), and common bacteria such as streptococci, mycoplasma, *Legionella*, *Listeria*, and salmonella. Vaccinations for influenza and pneumococcus are recommended but may have reduced efficacy in this population. Endemic organisms such as histoplasma and coccidiodes in the USA may also be seen. In general, the commonest infections reflect the commonest organisms prevalent in the recipient's environment—the fundamental difference between the transplant recipient and the general population is the rapidity of onset of symptoms and signs, the relative severity of infection, and the likelihood of coinfection with more than 1 pathogen.

A specific aspect particular to the transplant population is the issue of reactivation of latent infection and, also, the possibility of acquired latent infection from the donor. In common practice, this extends mainly to reactivations of CMV, varicella zoster, and herpes simplex virus. However, reactivations of tuberculosis, toxoplasmosis, and, in endemic areas, histoplasmosis and blastomycosis may occasionally present.[219-221]

In the pretransplant assessment of potential recipients, extensive serologic evaluation is performed to assess the patient's immune status regarding hepatitis viruses A, B, and C, CMV, Epstein-Barr virus (EBV), varicella-zoster, herpes simplex, human immunodeficiency virus, *Toxoplasma*, *Treponema pallidum*, and the measles virus. A tuberculin skin test is also performed. Vaccinations are then updated as necessary with hepatitis A or B vaccines, measles, or varicella-zoster vaccines. Tetanus toxoid, pneumococcal, and influenza vaccines are also updated as necessary.

At the time of transplantation, perioperative antibiotic administration is routine but may vary between institutions.[222-224] Administration of intranasal mupirocin calcium (Bactroban) ointment preoperatively is also usual and continued for some days postoperatively to eliminate nasal carriage of methicillin-resistant *Staphylococcus aureus*. This measure has been demonstrated to reduce the incidence of methicillin-resistant *S. aureus*-related infection postoperatively, including cardiac surgery.[225,226]

Postoperatively, prophylaxis against cytomegalovirus infection is routine, usually for a period of 3 months. As discussed in detail above, the

benefits of CMV prophylaxis include reduced incidence of acute and chronic rejection, and possibly of CAV infection and posttransplant lymphoproliferative disorder (PTLD) posttransplant.[227,228] Ganciclovir is the antiviral agent with efficacy against CMV that has been most extensively studied, and efficacy of ganciclovir in the prevention of CMV-related infection in solid organ transplant recipients has been demonstrated in smaller studies and in 1 meta-analysis.[229-231] The major side effect of ganciclovir is myelosuppression.[232] Ganciclovir has limited oral bioavailability, but oral ganciclovir is currently licensed for long-term CMV prophylaxis, with evidence of efficacy as maintenance therapy for solid-organ transplant recipients where it has been preceded by intravenous induction therapy.[177,233,234] Valganciclovir is a valine ester of ganciclovir, which has enhanced oral bioavailability and has proven efficacy as CMV pre-emptive therapy in cardiac transplant recipients.[235] It is rapidly hydrolyzed to ganciclovir, the active metabolite, through enzymes in the gut mucosa and hepatic cells. CMV resistance to ganciclovir (and valganciclovir) has been reported.[236-238] In these cases, foscarnet is used for CMV therapy but a major dose-limiting side effect of this agent is renal impairment.[232,239] Acyclovir has some efficacy against CMV suggested in a meta-analysis of 12 randomized trials.[240] Like ganciclovir, its oral bioavailability is limited but enhanced when delivered as its valyl ester, valacyclovir.[232] Valacyclovir is approved in some European countries for CMV prophylaxis.[232]

The transmission of *Toxoplasma gondii* is a concern in cardiac transplant recipients who are *Toxoplasma* antibody seronegative who receive an organ from a seropositive donor, as the *Toxoplasma* trophozoites or cysts reside in the skeletal and cardiac muscle of those previously infected. In this scenario, in the immunosuppressed state post transplantation there is a risk of local or disseminated toxoplasmosis. Therefore, it has been routine to administer antitoxoplasma prophylactic therapy to this group for at least 3 months, with either pyrimethamine, sulfadiazine, or folinic acid. This strategy has been challenged recently, as it has been shown that the rates of *Toxoplasma* reactivation in centers that do not employ antitoxoplasma prophylaxis at risk are negligible.[241] Efficacy for cotrimoxazole (trimethoprim-sulfamethoxazole) against *Toxoplasma* has also been shown and may be adequate prophylaxis against both *P. carinii* and *Toxoplasma*.[242,243] The practice in many institutions is to administer high-dose oral trimethoprim-sulfamethoxazole for 3 months and then to continue maintenance low-dose therapy for life for this purpose.
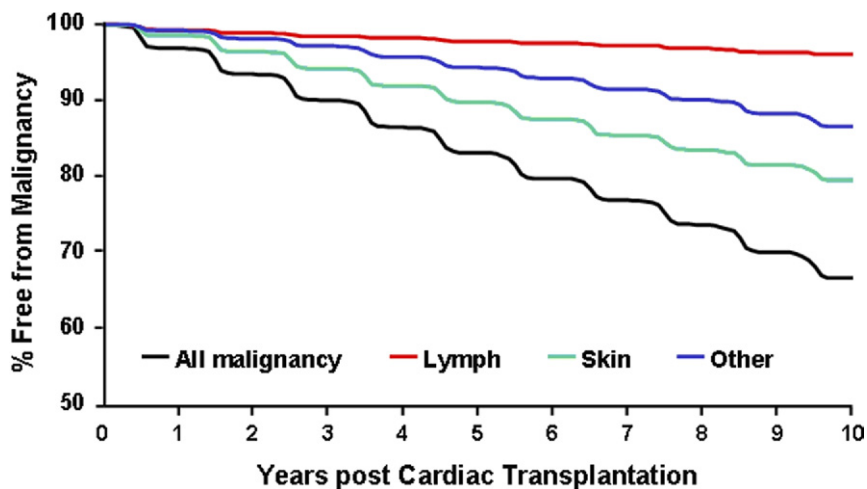
FIG 12. Cumulative data for freedom from malignancy (follow-ups: April 1994-June 2006: ISHLT 2007). (Color version of figure is available online.)

For cardiac transplant patients (as distinct from heart-lung and lung-transplant recipients), antifungal prophylaxis is not routine and not supported by data from clinical trials to date.[244]

Malignancy is a common complication of long-term immunosuppression.[245,246] Based on current ISHLT data, by 10 years post cardiac transplantation, the prevalence of malignancy is 33%.[73] Much of this is due to facilitation of chronic opportunistic infection by oncogenic viruses such as EBV for post transplant lymphoproliferative disorder, human herpes virus 8 in Kaposi sarcoma, and human papilloma virus for skin cancers.[247] All immunosuppressive agents have been implicated to some degree, with the possible exception of sirolimus, for which evidence is mounting that the risk of malignancy may be significantly lower.[213,248] Most of these cancers are skin-related (61%); the remainder are solid tumors including prostate, lung, bladder, breast, cervical, renal (total, 18%) and lymphoproliferative, including PTLD (6%).[72] (Fig 12).

Skin cancer is a common cause of morbidity and rarely mortality post transplant and in the transplant recipient is often recurrent and more aggressive.[246,249,250] One series reported the relative risk of developing skin malignancy for a solid organ transplant recipient as greater than 100 compared with that of the general population.[251] Cardiac transplant recipients are probably at higher risk of development of skin malignancy compared with renal transplant recipients due to the higher threshold of immunosuppression required.[252] The risk of skin malignancy may vary

with different immunosuppressive regimens; recent evidence has suggested that cyclosporine may have a specific carcinogenic effect independent of its immunosuppressive effect[253] and the use of sirolimus as an alternative agent may be protective and may even induce remission of skin cancers in transplant recipients.[254-256] The appropriate response of transplant physicians confronted with recurrent skin malignancy has been to reduce immunosuppression. There have been numerous series showing efficacy for these measures and these have recently been comprehensively reviewed.[257] Guidelines have been proposed for gradual reduction of immunosuppression based on elevated skin cancer risk,[258] which continue to be further defined.[259] The importance of patient education and specialist advice regarding appropriate risk-reducing measures cannot be underestimated.[260] The role of retinoids in the prevention of skin malignancy in this population remains under review; initial results have been encouraging. However, the limiting factor is patient tolerability.[261,262]

Solid tumors in cardiac transplant recipients are relatively common, and the small number of series that have looked at the incidence of solid tumors in transplant patients has found that lung cancers are most frequent.[263,264] Lung malignancy in the cardiac transplant recipient carries a very poor prognosis; most patients present with already advanced disease and one series reported a median survival after diagnosis of only 27 days.[264] This strongly suggests that these cancers pursue a more aggressive course in the immunosuppressed patient. Not surprisingly, a history of smoking in the years preceding cardiac transplantation correlated with an increased chance of development of malignancy post transplantation.[263] Urological malignancy including prostatic carcinoma is next most common in male patients and cervical carcinoma in females, followed by Kaposi sarcoma and nonlymphoproliferative head and neck malignancy.[263,265]

PTLD was first described by Israel Penn in 1969 as lymphoma occurring as a complication of azathioprine therapy.[266] The terminology was later changed to PTLD in 1984 as the pathology is highly variable and often very different from that of lymphoma.[267-272] EBV infection has been very strongly associated with the development of PTLD[273]; however, the risk of developing this condition is multifactorial and related to immunosuppression and impaired T-cell immunity in the setting of foreign antigenicity from the transplanted organ.[274] No particular immunosuppressive drug has been implicated more than others[274,275] except where very high-dose cyclosporine was used as a substitute for azathio-

prine.[275] A significant minority of PTLD malignancies are EBV negative, and these may present in later years post transplantation and may be associated with a poorer prognosis.[274,276-278] Other risk factors that have been identified are younger recipient and donor age (<18 years)[275,279] and more than 5 acute rejection episodes post transplantation.[275] CMV infection has also been considered as a risk factor.[280] The evidence for a protective effect of antiviral prophylaxis on the development of PTLD is mixed and inconclusive overall.[275,281-283]

The largest series available on PTLD comes from the Israel Penn International Transplant Tumor Registry based at the University of Cincinnati, OH.[276] From their data on 274 cardiac transplant patients with PTLD, they reported a 50% mortality within 1 year. Ninety percent of cases were EBV-positive and a similar percentage was B-cell-predominant. The commonest sites involved were the lung and lymph nodes (34% and 32%), followed by the gastrointestinal tract (24%), liver (23%), central nervous system (13%), spleen (11%), and the cardiac allograft itself (10%). PTLD in the transplant heart has been reported by others,[284,285] and more unusual locations for PTLD have also been described such as the skin,[286,287] the pleura,[288] breast tissue,[272] and even in gingival tissue mimicking cyclosporine-induced gingival hyperplasia.[289] PTLD may also involve the transplanted heart itself.[290] The potential for PTLD to present in these unusual locations underlines the importance of obtaining a tissue sample for analysis wherever possible when the diagnosis is in doubt. In this respect fine-needle aspiration biopsy has been shown to be highly sensitive and specific.[291]

The treatment of PTLD is based largely on evidence of a small number of patients for the efficacy of various strategies. There have been no randomized controlled clinical trials to date of any interventions currently in use. The first strategy usually employed is minimization of imunosuppressive therapy. Most patients with PTLD are usually heavily immunosuppressed and a significant reduction in immunosuppressive therapy is usually possible. The next step is usually anti B-cell monoclonal antibody therapy, most frequently given as rituximab, an anti-CD20 monoclonal antibody, which has had efficacy shown in small studies.[292-294] Another modality that has been used with success in a small number of patients is anti-IL-6 antibody therapy.[295] Some institutions employ monoclonal antibody therapy only if reduction in immunosuppression fails; in others its use is routine, in particular if PTLD occurs early in the post-transplant course and a significant reduction in immunotherapy cannot be contemplated. Failing treatment with rituximab

(which is often the case if the tumor does not express CD20) requires salvage chemotherapy, and use of this strategy has recently been described in a small study.[296] A new but promising strategy, adoptive immunotherapy for PTLD, involves the administration of banked HLA-matched or autologous-cloned EBV-specific cytotoxic T-cells.[297] This strategy remains under evaluation, but results of the first phase 2 multicenter clinical trial have been encouraging.[298]

Conclusions

Cardiac replacement therapy in end-stage heart failure is at a crossroads. The art and science of cardiac transplant medicine has been perfected since the first transplant in 1967 and outcomes continue to improve. However, the number of transplants being performed worldwide is far outnumbered by the number of potential candidates, as donor hearts are a very limited resource. Advances in destination device therapy may provide a viable long-term solution for many patients, with either support of the native heart by LVAD therapy or even possibly complete replacement of the heart by a prosthetic device. Completely implantable devices that offer the patient as normal a life as possible with a minimal risk of infection are likely to have the greatest impact in this field. Advances in xenotransplantation in nonhuman primate models are encouraging, with the possibility of clinical trials in the future. The potential of cell therapy is still under evaluation and the field is still in its infancy but rapidly evolving; the key to the future in this field may not be the delivery of the cells themselves but understanding how they interact with one another at a molecular level and, in particular, with resident stem cells in cardiac tissue. New insights in this field could potentially herald a new era in pharmacotherapy for this devastating condition.

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