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Ventricular replacement therapy for heart failure

R. Bogaev

INTRODUCTION

Cardiac transplantation remains the treatment of choice for ventricular replacement in patients who suffer from end-stage heart failure. Unfortunately, this type of therapy has been limited to merely 2200 recipients each year due to a dwindling donor pool and patient ineligibility from advanced age and comorbidities. Patients are more likely to die while awaiting heart transplantation than in the first 2 years following cardiac transplantation. Although xenotransplantation is technically feasible, societal, ethical, immunological, and infectious implications remain controversial barriers to this as an alternative biological replacement therapy. Steadily improving outcomes and efficacy with ventricular assist device (VAD) implantation in bridging patients to cardiac transplantation ushered in the application of mechanical circulatory support (MCS) as permanent ventricular replacement or destination therapy (DT) for the growing incidence of end-stage heart failure. In 2003, the Centers for Medicare and Medicaid Services and the Food and Drug Administration (FDA) approved left VADs (LVADs) for patients who meet certain inclusion criteria and are deemed ineligible for cardiac transplantation based on the results of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial. Only more recently, LVAD therapy been increasingly used as DT rather than as the traditional bridge to transplantation. Updated data from the DT registry highlights the importance of patient selection and risk stratification for DT. Low-risk patients who receive implants before the appearance of end-organ failure have significantly increased survival rates that rival those seen at 1-year post-cardiac transplantation. Strategies to augment DT success furthermore include optimizing patients' hemodynamics prior to VAD implantation, aggressive nutritional support, infection prevention, and right heart failure management. Multidisciplinary teams in the manufacturing industry are closely collaborating to develop improved designs, in particular smaller device size, increased durability, and improved biocompatibility. These improvements will soon afford more patients the option of ventricular replacement for end-stage heart failure.

In 1953, Dr John Gibbon [1], inventor of the cardiopulmonary bypass (CPB) machine launched the modern era of MCS when he utilized the CPB machine to correct an atrial septal defect (ASD) in an 18-year-old girl. After undergoing several modifications, the CPB machine revolutionized cardiac surgery [2].

The first cardiac allotransplant was performed by Dr Christiaan Barnard in December 1967. The initial worldwide enthusiasm for this landmark surgical success was soon tempered

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Table 15.1 Acute heart failure hemodynamics warranting consideration of MCS (with permission from [8])

■ Cardiac index <2 l/min
■ Systolic blood pressure <90 mmHg
■ Left or right atrial pressure >20 mmHg
■ Systemic vascular resistance >2100 dynes/s/cm

by early immunosuppressive complications and the limitations of long-term immunosuppressive agents. Infection and drug toxicity cascaded in a catastrophic 1-year survival rate of approximately 15%. By the 1970s, only two transplant centers, Stanford and the Medical College of Virginia, continued to pursue cardiac allotransplantation as a therapeutic strategy for cardiac replacement. Notwithstanding, the disappointment with cardiac transplant fueled a renewed quest for a long-term mechanical device as a replacement for the failing heart [3].

The Artificial Heart Program was established in 1964 by the National Heart Institute (now the National Heart, Lung, and Blood Institute, or NHLBI, reflecting expansion of functions) to promote the development of a total artificial heart (TAH) and other cardiac assist devices through the creation of research grants and contracts. In 1970, The Artificial Heart Program became the Medical Devices Application Branch of the National Heart and Lung Institute (NHLI). The objectives of the program were to develop cardiac assist systems to treat acute circulatory insufficiency, bridge patients to stabilization or recovery, or provide permanent support for the remainder of the patient's life, and to develop a totally implantable artificial heart to replace an irreversibly damaged heart [4]. John Watson, director of the Devices and Technology Branch of the NHLBI, issued two requests for proposals in 1977: one for the development of 'Left Heart Assist Pumps' [5] and the other for the 'Development of Electrical Energy Converters to Power and Control Left Heart Assist Devices' [6]. A third request for proposal was issued in 1980 for 'Development of an Implantable Integrated Electrically Powered Left Heart Assist System' to provide patient support in excess of 2 years [7]. The initial awardees of these requests, ABIOMED Inc., Baxter Healthcare, Thermo Cardiosystems Inc., and Thoratec, developed the first generation of left ventricular assist systems, which built the foundation for modern day devices in the field of MCS [4].

In the setting of acute heart failure, hemodynamic criteria warranting consideration of MCS include a cardiac index <2 l/min, a systolic blood pressure <90 mmHg, left or right atrial pressure >20 mmHg, and a systemic vascular resistance >2100 dynes/s/cm [8] (Table 15.1). However, these criteria do not accurately reflect the state of decompensation in those patients with chronic heart failure. The ability to achieve optimal outcomes is predicated by recognition of the patient's compromised hemodynamics and prompt referral to a center that offers MCS. In accordance with the objectives of the Artificial Heart Program, three major indications have emerged for MCS. The first indication is in patients whose ventricular function is anticipated to recover after a medium to short period of support. These patients, including those with acute viral myocarditis, acute myocardial infarction, or post-cardiotomy shock despite viable myocardium, are referred to as the *bridge to recovery* patients. Once hemodynamic stability has been restored, patients should be treated with optimal medical therapy, including ACE inhibitors, β-blockers, and aldosterone antagonsists, to enhance the opportunity to reverse remodel their native hearts. Sir Magdi Yacoub demonstrated unparalleled success in bridging patients to recovery with his unique combination strategy of LVAD support to produce maximal unloading, standard medical therapy to produce maximal reverse remodeling, and pharmacologic therapy with clenbuterol, a selective β_2-adrenergic receptor agonist, to induce adaptive physiologic cardiac hypertrophy (the Harefield protocol) [9]. Following a period of myocardial unloading and optimization with standard medical therapy, the patient is weaned from the LVAD either at the

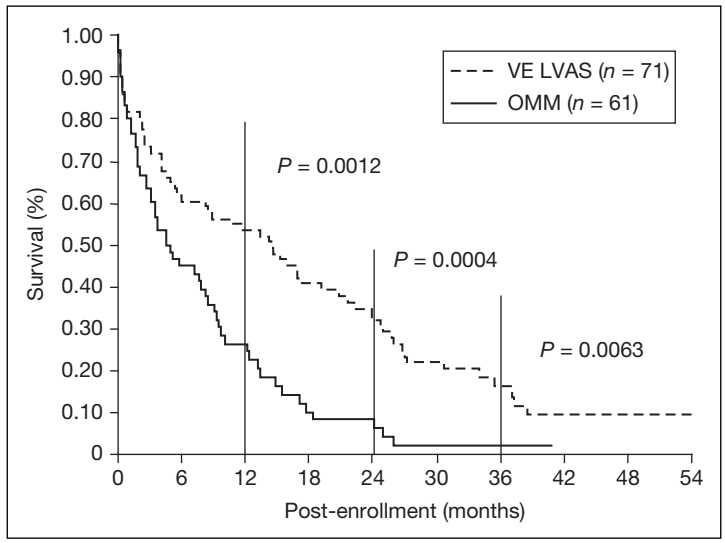

Figure 15.1 Mortality in patients who received the HeartMate® LVAS for DT vs patients randomized to optimal medical management (OMM). With permission from [12].

bedside or in the operating room under echocardiographic guidance. If the myocardial function remains preserved in the face of weaning support, the device may be explanted. If the patient develops hemodynamic instability or recurrent myocardial depression after device removal, a device for longer-term support should be implanted [10].

The second indication, known as *bridge to transplantation*, stabilizes those patients with progressive chronic heart failure who are actively awaiting cardiac transplantation. Patients are referred for LVAD support to prevent systemic effects of worsening heart failure such as progressive deterioration in renal function, development of pulmonary hypertension, or right heart failure with congestive cirrhosis, all of which can lead to ineligibility for cardiac transplantation. Patients with ventricular arrhythmias refractory to medical therapy and those with incessant defibrillator firings also benefit greatly from LVAD implantation. In light of the ACC/AHA guidelines which recommend avoiding continuous inotropic support with the exception of palliative care, transplant centers are initiating the use of MCS as a *bridge to transplantation* once patients are declared as inotrope-dependent [11].

The third indication is the use of an implantable LVAD as permanent therapy *or DT*. In a landmark study, the REMATCH trial demonstrated a 48% reduction in mortality in patients who received the HeartMate® LVAS for DT vs patients randomized to optimal medical therapy [12] (Figure 15.1). On 1 October 2003, the Center for Medicare and Medicaid Services approved DT for patients who meet criteria established by the REMATCH trial and who are deemed ineligible for cardiac transplantation [13]. The criteria require Stage C–D heart failure with NYHA class IV symptoms, LVEF $<25\%$, a peak oxygen consumption <12 ml/kg/min, and a life expectancy <2 years. Additionally, patients must have significant functional limitations that are refractory to treatment with maximally tolerated doses of drugs, as outlined in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, for at least 60 of the 90 days before device implantation [12] (Table 15.2).

Appropriate patient selection has become paramount in achieving successful outcomes with VAD therapy. Multiple pre-operative risk scoring systems and criteria aid in identifying those patients for which VAD implantation would be contraindicated. Risk scoring can

Table 15.2 Eligibility criteria for destination therapy (with permission from [12])

- Stage C–D heart failure
- NYHA class IV symptoms
- LVEF <25%
- Peak oxygen consumption <12 ml/kg/min
- Life expectancy from heart failure <2 years
- Significant functional limitations, refractory to maximal medical therapy for at least 60 of the last 90 days

also guide the optimization of patients' conditions prior to surgery. In 1994, Swartz and colleagues [14] at St Louis University reported the use of 21 clinical variables, defining the patients' hemodynamic status, evidence of end-organ function, and hemostasis, to allocate patients into three different risk groups. The lowest-risk group had a survival rate of 100%, while 53% of the moderate-risk group and only 36% of the highest-risk group survived. Although this scoring system ignores factors such as previous open heart surgeries and the presence of diabetes, the stratification into high-, moderate-, and low-risk groups allows both the patient and the medical team a more realistic appreciation of the expected outcome with VAD therapy.

The first scoring system to predict more accurately which patients would have successful outcomes after LVAD implantation was developed in 1995 by investigators at the Cleveland Clinic Foundation and Columbia University. This LVAD screening score was revised in 2001 to reflect five clinically significant factors: ventilatory support, reoperative surgery, previous LVAD insertion, central venous pressure >16 mmHg, and prothrombin time >16 s. An LVAD score >5 correlates with a post-operative mortality of 47%; in contrast, a score ≤5 yields a post-operative mortality of 9% for those with a score <5 [15].

Lietz *et al*. [16] reviewed data on 195 LVAD patients enrolled in the Thoratec DT registry between November 2001 and March 2005. By univariate analysis, significant pre-operative risk factors for 30-day mortality included reflections of the severity of heart failure: serum Na <135 mmol/l, central venous pressure >10 mmHg, and systolic blood pressure <90 mmHg; evidence of end-organ dysfunction: aspartate aminotransferase >90 units/l, alanine transaminase >90 units/l, total bilirubin >1.3 mg/dl, and creatinine clearance <30 ml/min or serum creatinine >2.0 mg/dl; markers of malnutrition such as recipient body mass index <27 kg/m^2 or serum albumin <3.3 g/dl; hematologic abnormalities including white blood cell count >12 000/mm^3, platelet count <200 000/mm^3, and Hct <35%; recipient size: <80 kg, and advanced age >65 years. When DT candidates were stratified by the pre-operative risk score into extremely high-, very high-, high-, moderate- and low-risk categories, the 2-year survival ranged from 0%, 27.2%, 30.3%, and 54.2% to 72.4%, respectively [16] (Figure 15.2). To achieve optimal outcomes with VAD therapy, it is critical to adequately assess and optimize a patient's hemodynamic status, renal and hepatic function, nutrition, and coagulation as well as to mitigate inflammation and resolve any underlying infections. Although scoring systems assist in patient selection, each review is limited by the small number of patients included in the analysis. It is therefore difficult to firmly establish relative contraindications at this time. The ultimate decision to proceed with VAD implantation can only be made after a thorough assessment of the patient and all attempts to optimize the patient's hemodynamics and end-organ function.

Irreversible neurological injury, sepsis, irreversible renal failure, and uncorrectable hepatic dysfunction have emerged as absolute contraindications to VAD insertion. In the setting of cardiogenic shock, it may be initially impossible to determine all irreversible factors. Short-term support with either an intra-aortic balloon pump or percutaneous VAD will allow time to assess recovery of end-organ function. Those patients who develop acute

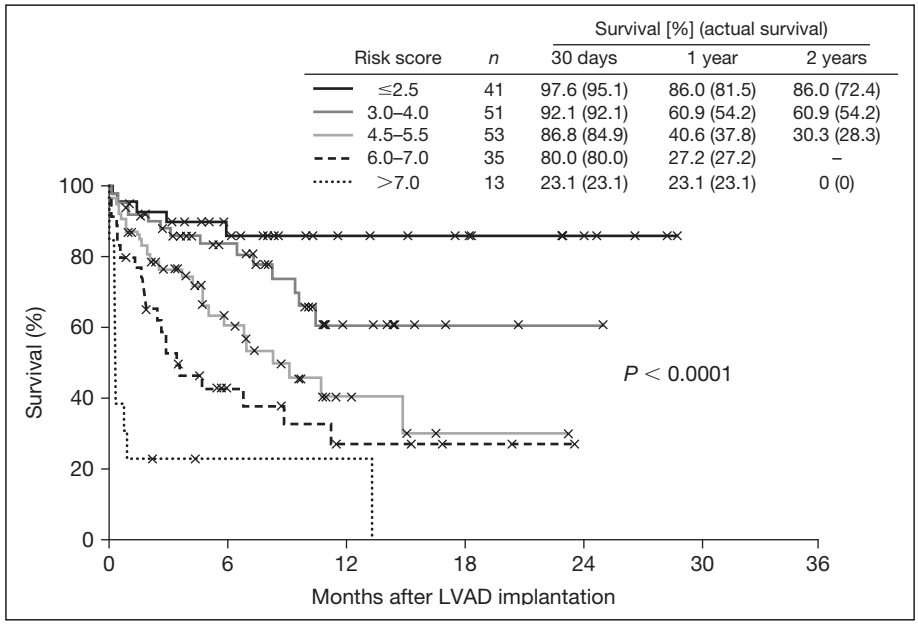

Figure 15.2 Two-year survival after LVAD implantation when DT candidates were stratified by the pre-operative risk score into extremely high, very high, high, moderate and low risk categories. With permission from [16].

renal failure and require hemodialysis post-operatively experience a higher incidence of LVAD infections due to the inherent need to maintain vascular access [9].

REMATCH identified infection, sepsis, bleeding, and mechanical device failure as the four major causes of death in the LVAD cohort. Pre-operative optimization of patients begins with a thorough analysis of the laboratory data to identify those with impending end-organ dysfunction [17]. Patients who remain volume overloaded should be diuresed aggressively in anticipation of reducing over distension of the right ventricle and decreasing hepatic congestion. Coagulation derangements are common and reflect the use of antiplatelet or anticoagulant therapy, nutritional deficits, and hepatic congestion. Screening for coagulopathy should include assessment of the prothrombin time, international normalized ratio, partial thromboplastin time, platelet count, platelet aggregation studies, and a bleeding time. Patients who have been exposed to heparin and most notably those who have undergone cardiac surgery should be screened for the development of heparin antibodies, which will predispose them to heparin-induced thrombosis and thrombocytopenia with re-exposure to heparin. Hyperbilirubinemia with elevated total bilirubin levels >3.6 mg/dl or direct bilirubin levels >1.2 mg/dl is an independent risk factor for death [18]. Great efforts must be made to correct the coagulation parameters and bilirubin levels before surgery.

Chronic renal insufficiency and anemia that is responsive to erythropoietin therapy are extremely common in patients with end-stage heart failure who may be candidates for VAD therapy. Inotropes, vasodilators, and a concomitant intra-aortic balloon pump should be used to augment the cardiac output to >2.0 l/min, reduce filling pressures to a CVP <12 mmHg and pulmonary capillary wedge pressure (PCWP) <24 mmHg, and increase renal blood flow to achieve a CrCl >30 ml/min.

Nutrition is one of the most under-valued aspects of a patient's pre-operative status, yet it is one of the most powerful predictors of post-operative mortality [19]. Poor nutrition portends poor wound healing and impaired T-lymphocyte function, predisposing the patient to

a VAD infection. Screening for malnutrition entails testing of the serum albumin, pre-albumin, transferrin, and retinol binding protein levels. It is judicious to invest a few weeks into improving the patient's overall nutritional state through the use of multi-dose daily protein shakes or even continuous tube feeding [19]. On the other hand, those patients who are hemodynamically unstable or who develop systemic inflammatory response syndrome (SIRS) may not be able to tolerate tube feedings until they achieve hemodynamic restoration.

Infection was cited as the most common cause of mortality in the REMATCH trial, accounting for 41% of LVAD patient deaths. Infection prevention begins with proper patient selection and the good clinical practice of hand hygiene, and it continues with the prevention of surgical site infection, catheter-related bloodstream infection, and healthcare-associated pneumonia as outlined on the Centers for Disease Control and Prevention website [20]. Thoratec's Guidelines for Pre-operative Infection Prevention promote the administration of antibiotic prophylaxis customized per institutional flora and susceptibility patterns. The patient's nasal passages are cultured pre-operatively to identify colonization of methicillin-resistant *Staphylococcus aureus*. If the culture is positive, administration of mupirocin 2% nasal ointment is given twice daily (BID) for a 5-day course, starting the evening prior to surgery [21]. Adherence to these guidelines has lowered the sepsis-related death rate in DT patients at four high-volume institutions by 8.3 times [22].

Once the patient has been assessed for risk and all attempts have been made to optimize the patient's status, the team must select the most appropriate device to meet the patient's needs. Device selection is invariably influenced by the devices available at each institution, the physicians' and nurses' experience, and the clinical indication, as well as the patient's requirement for biventricular or univentricular support. The FDA has approved selected devices for all three clinical indications: bridge to recovery, bridge to transplantation and DT. Devices approved for *bridge to recovery* include ABIOMED's BVS® 5000 and AB 5000 Ventricle, and Thoratec's VAD and implantable VAD (IVAD™). For *bridge to transplantation*, the Thoratec® VAD, IVAD™, HeartMate® IP and XVE LVAD, Novacor® LVAS and CardioWest™ TAH are FDA-approved systems. The only device currently approved for *DT* is the HeartMate® XVE LVAD. A number of investigational devices, including the new-generation axial flow pumps – Jarvik 2000, HeartMate® II, and MicroMed DeBakey VAD® – are presently undergoing clinical trials and promise to expand and augment the clinical application of MCS.

Percutaneous MCS may be included as a component in the patient's pre-operative optimization to restore normal hemodynamics and improve end-organ function. The TandemHeart® Percutaneous Transseptal Ventricular Assist (PTVA®) system (CardiacAssist Inc., Pittsburg, PA) has a 510K approval by the FDA for temporary ($\leq$6 h) left ventricular bypass. This continuous centrifugal pump can deliver up to 4 l/min of flow by diverting blood from the left atrium to the systemic circulation. A 21-F inflow cannula is inserted into the left atrium *via* a standard trans-septal puncture through a femoral venous sheath and a 15-F or 17-F outflow cannula placed in the femoral artery. Results from a trial that enrolled 18 patients with cardiogenic shock revealed a significantly reduced mortality rate of 41% compared to the 60% seen in the SHOCK trial registry [23]. The TandemHeart PTVA has also been used in selected cases at some institutions to support the right ventricle. For this application, a 21-F cannula is placed in the right atrium *via* the left femoral vein or subclavian vein, and a 21-F outflow cannula is placed over a guidewire into the main pulmonary artery from either a right internal jugular or a right femoral vein approach (Figure 15.3).

The BVS 5000 (ABIOMED Inc., Danvers, MA) is a short-term extracorporeal system composed of two polyurethane blood sacs separated by polyurethane valves. The device uses gravity to fill a pneumatic pump and eject blood. This straightforward engineering design eliminates the need for continuous monitoring by a perfusionist (Figure 15.4). The BVS 5000 was the first FDA-approved device for bridge to recovery for patients with reversible heart failure and has been widely used at over 600 institutions globally. The ease

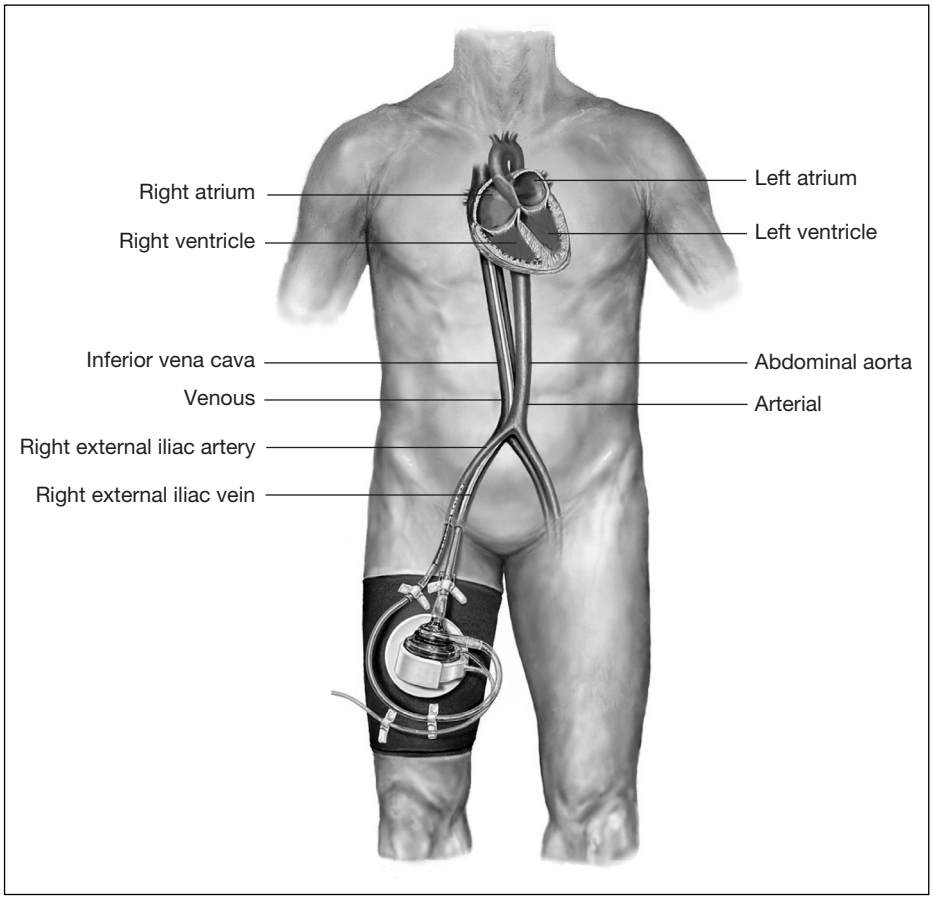

Figure 15.3 TandemHeart® Percutaneous Transseptal Ventricular Assist (PTVA®) System (CardiacAssist, Inc., Pittsburg, PA).

of insertion has generated the 'spoke and hub phenomenon', whereby the pump may be implanted at a non-transplant center and the patient subsequently transferred to an advanced cardiac center with the options of cardiac transplantation or DT. Most patients are supported for 5–7 days, after which point a decision to wean or convert to longer-term support is made. ICU monitoring, limited ability for patients to ambulate, and the need for continuous IV anticoagulation are placing this system at a disadvantage. However, a recently reported 10-year experience with the ABIOMED BVS at Columbia University revealed an overall 62% patient survival rate [24].

The AB 5000 Circulatory Support System (ABIOMED Inc., Danvers, MA) was approved by the FDA as an adjunct to the BVS system for short to intermediate support as a bridge to recovery (Figure 15.5). The AB 5000 ventricle is powered by a portable partial vacuum and partial pneumatic console, allowing patients to ambulate. This paracorporeal device uses the same cannulae as the BVS 5000 blood pump, thereby facilitating the transition from the BVS to the AB device when longer-term support is required. Hemolysis due to the presence of high-velocity flow at the inlet cannula was initially reported by the Texas Transplant Institute [25] but can be avoided with transesophageal guidance to prevent turbulence at the

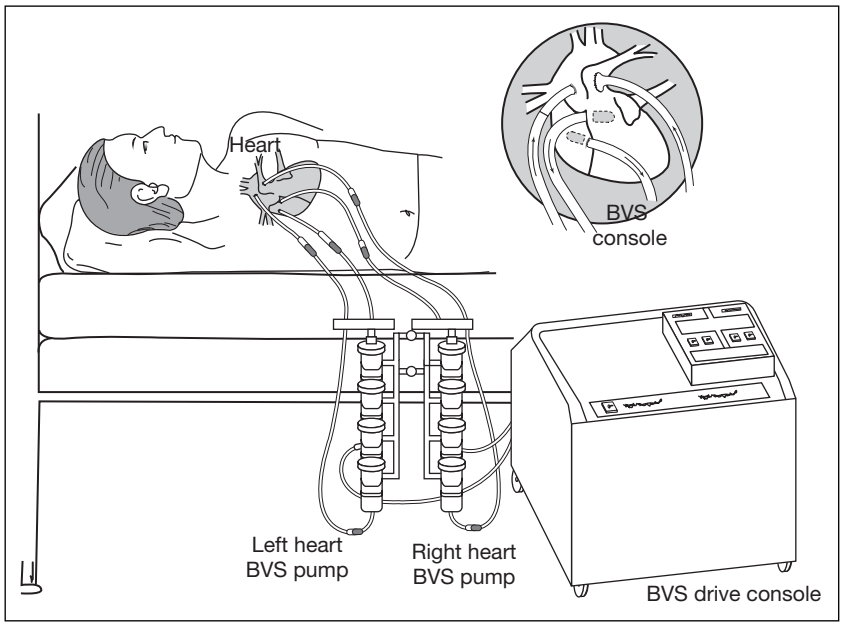

Figure 15.4 BVS® 5000 Blood Pumps (ABIOMED Inc., Danvers, MA).

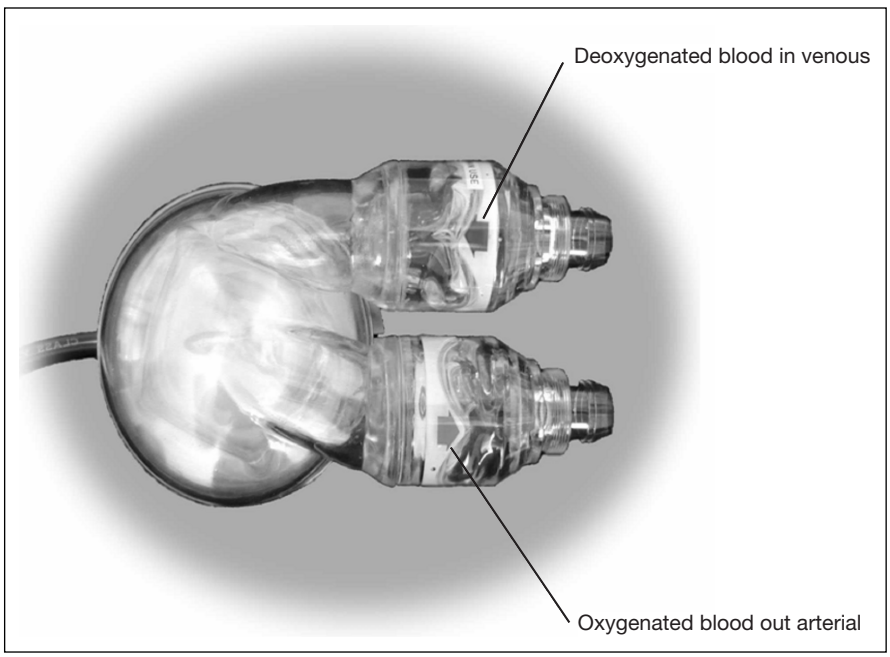

Figure 15.5 AB 5000 Ventricle (ABIOMED Inc., Danvers, MA).

Figure 15.6 Levitronix® CentriMag® Blood Pumping System (Levitronix® Inc., Waltham, MA).

inflow cannula at the time of cannula placement. The AB 5000 console has subsequently been made to allow for adjustable vacuum if hemolysis develops following implantation.

The Levitronix® CentriMag® Blood Pumping System (Levitronix Inc., Waltham, MA) is designed to provide MCS for up to 14 days for patients suffering from severe, acute, but potentially reversible, cardiac failure. The magnetically levitated impeller in this pump eliminates the need for seals and bearings, which are known to cause hemolysis and promote thrombus formation (Figure 15.6). Because this design also avoids the use of flexing sacs, diaphragms, or valves, which are known to be prone to failure and thereby extends the longevity and reliability of the device. The CentriMag Short-Term Left Ventricular Assist System is FDA approved in the US for investigational use only but is CE-mark approved and commercially available throughout Europe [26].

The Thoratec VAD (Thoratec Corporation, Pleasanton, CA) is a commonly used pulsatile pump that consists of two mechanical valves and a polyurethane blood sac. The Thoratec VAD is FDA approved for bridging patients to recovery or transplantation. The paracorporeal position has facilitated left, right, or biventricular support of more than 2800 patients weighing from 17 kg to 144 kg (Figure 15.7) [27, 28]. An initially large and cumbersome console has been updated with a briefcase-sized TLC-II portable driver to allow patients to be discharged home while awaiting cardiac transplantation. Of note, the mechanical valves require patients to be on chronic anticoagulation therapy with warfarin. Longer waiting times have stimulated the design of an implantable iteration of the paracorporeal VAD. The Thoratec implantable VAD (IVAD), approved by the FDA in August 2004 for bridging to transplantation or treating post-cardiotomy shock, is about half the size of the paracorporeal version and has a smooth, polished, and contoured titanium alloy housing (Figure 15.8). A sensor on the TLC-II portable driver detects adequate filling and emptying of the blood sacs. The IVAD is versatile and can be used in either the paracorporeal or implantable position, as well as to support the left, right, or both ventricles [27]. El-Banayosy *et al*. [29] reviewed their experience with 104 patients supported by the Thoratec paracorporeal VAD. Although patients requiring biventricular support had worse outcomes than those who only needed univentricular support, powerful predictors of overall poor outcome included

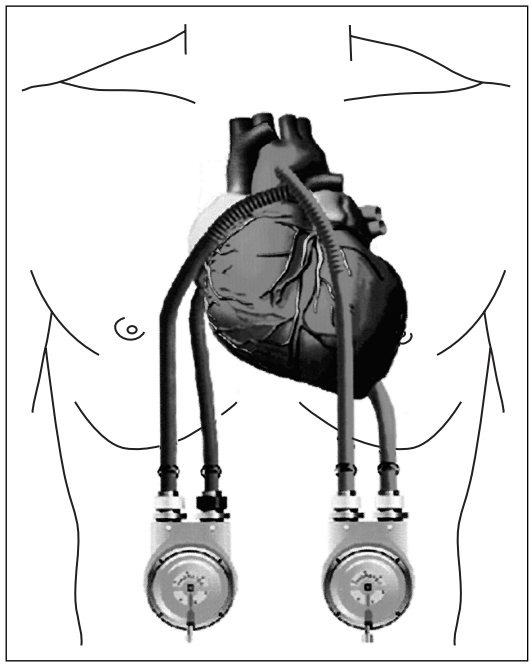

Figure 15.7 Thoratec® Ventricular Assist Devices (Thoratec Corporation, Pleasanton, CA).

pre-implant mechanical ventilation, hyperbilirubinemia, and age >60 years old. El-Banayosy's experience at Bad Oeynhausen highlights the importance of careful patient selection in achieving success with MCS.

The HeartMate® Left Ventricular Assist System (Thoratec Corporation, Pleasanton, CA) was initially FDA approved in 1994 as an implantable pneumatic (IP) device in bridging patients to transplantation. A more portable system with wearable batteries, the vented electric (VE), received FDA approval for commercial use in 1998. The most recent iteration, the XVE, which has a newly designed inflow valve, was FDA approved for bridge to transplantation in 2002 and subsequently approved for DT in 2003 [30]. Improvement in pump design, patient selection, and peri-operative management translated into improved survival, from 63.5% to 72.4%, when bridging patients to transplantation at Columbia University [31]. The HeartMate® is a simple pusher-plate pump with a diaphragm separating the blood compartment and air chamber. Titanium microspheres on the surface of the pump and textured polyurethane covering the flexible diaphragm promote the formation of a pseudo-intimal layer along the blood-contacting surfaces, obviating the need for chronic anticoagulation (Figure 15.9). Conversely, the textured surface has also been associated with the development of preformed reactive antibodies (PRAs) and T-cell dysfunction [32]. The Cardiac Transplant Research Database Research Group reviewed patients who received transplants from 1990 to 1997. Despite concerns about the elevated PRAs in VAD patients, Kaplan-Meier and multivariate Cox regression analyses showed no significant difference in post-transplant survival between the LVAD and medical therapy groups [33]. The HeartMate IP and XVE have been associated with very low thromboembolic rates of 3% and 6% respectively [34, 35]. Nonetheless, patients on the HeartMate LVAS may require chronic anticoagulation for other reasons such as atrial fibrillation, a hypercoaguable state, or the presence of a ventricular thrombus. The pump housing can be implanted in either a pre- or an intra-peritoneal position

Figure 15.8 Thoratec® Implantable Ventricular Assist Device (IVAD™) (Thoratec Corporation, Pleasanton, CA).

Figure 15.9 HeartMate® XVE Left Ventricular Assist System (Thoratec Corporation, Pleasanton, CA).

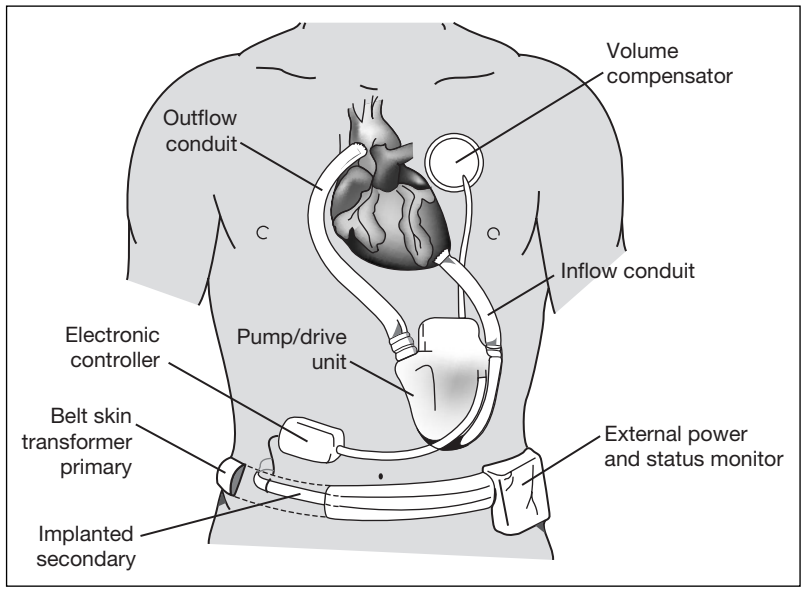

Figure 15.10 Novacor® Left Ventricular Assist System (World Heart Corporation, Ottawa, Ontario, Canada).

in the left upper quadrant with an external drive line, consisting of an air vent and electrical cable, traversing the abdomen to exit the skin in the right upper quadrant. This bulky pump is limited to patients with a body surface area (BSA) of $>1.5\,m^2$. The HeartMate XVE remains the only device approved for DT. Growing experience with patient selection and management, as well as improvements in the HeartMate XVE LVAS, have allowed centers to improve outcomes to a level approaching those seen with cardiac transplantation [22].

The Novacor (World Heart Corporation, Ottawa, Ontario, Canada) LVAS is an implantable, wearable, pulsatile device that was first used at Stanford University in 1984 to bridge a patient to transplantation. Today, the Novacor® LVAS, implanted in more than 1600 patients, is the only MCS device to support a single patient for more than 6 years, thus earning its reputation as the most durable pump on the market (Figure 15.10) [36]. In this particular pump, dual pusher-plates compress a polyurethane sac, thereby ejecting blood into the aorta. Bioprosthetic valves are featured in the inflow and outflow grafts. The Novacor has been associated with thromboembolic events related to particulate matter in the inflow graft. Transitioning to an expanded polytetrafluoroethylene (PTFE) inflow conduit has decreased the embolic cardiovascular accident (CVA) risk to <10% by eliminating pannus formation along the inflow tract [36]. However, Novacor LVAS patients still require chronic anticoagulation with warfarin. Like the HeartMate, the pump is placed either in a pre-peritoneal pocket or the intra-peritoneal space, with a drive line tunneled across the lower abdomen and exiting in the right upper quadrant. For this reason, the device also requires a BSA of $>1.5\,m^2$. Baran *et al*. [37], at Newark Beth Israel Medical Center, reviewed their cumulative experience with the Novacor LVAS as a bridge to transplantation. Twenty-six of 39 patients survived to transplantation with post-transplant survival rates of 80.4%, 75.7%, and 64% at 1, 3, and 10 years, respectively. In contrast to other VAD patients, those supported with the Novacor LVAS did not experience an increase in PRAs following VAD implantation, and they had rejection profiles after transplantation equivalent to those of non-VAD patients. The results of the Investigation of Non-Transplant Eligible Patients who are Inotrope Dependent (INTrEPID) feasibility study presented at the 2005 American

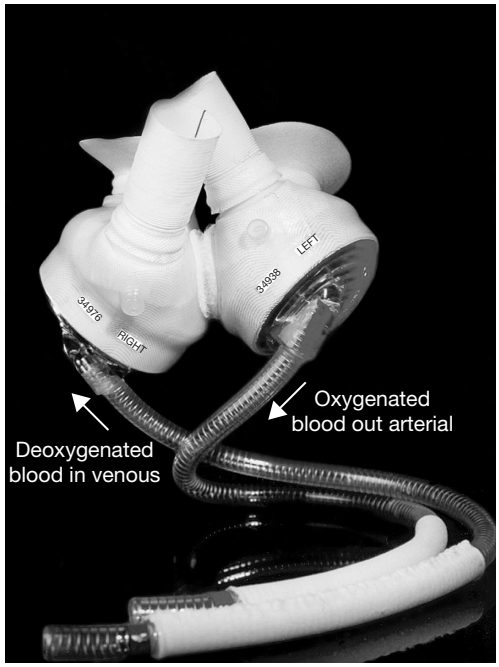

Figure 15.11 CardioWest™ Total Artificial Heart (SynCardia Systems, Tuscon, AZ).

Heart Association Scientific Sessions revealed an improved quality of life and improved survival among patients who received the Novacor LVAS vs those who were randomized to optimal medical therapy [38]. Following the INTrEPID study, World Heart began conducting the Randomized Evaluation of the Novacor LVAS In a Non-Transplant Population (RELIANT) trial to establish that the Novacor LVAS is superior to optimal medical therapy and equivalent to the HeartMate XVE for DT. The trial was later halted because of slow enrollment and clinicians' preferene for smaller, continuous-flow pumps.

The CardioWest™ TAH (SynCardia Systems, Tuscon, AZ) received FDA approval for temporary support to bridge patients to transplantation [39]. The CardioWest is a pneumatic pulsatile biventricular implantable system that replaces the native ventricles and all four valves in patients who are at risk of imminent death from biventricular failure (Figure 15.11). The device consists of two polyurethane chambers with a four-layer, pneumatically driven diaphragm, inflow and outflow conduits containing Medtronic Hall valves, and an externalized drive line. In the US, the CardioWest TAH is powered by a large console that tethers patients to the hospital, whereas facilities in Europe currently utilize portable drivers, which permit discharge from the hospital. A TAH may benefit patients with relative contraindications for an LVAD, including aortic regurgitation, intractable cardiac arrhythmias, and the presence of a left ventricular thrombus, a ventricular septal defect, or irreversible biventricular failure. A non-randomized prospective study conducted at five centers with the use of historical controls was performed to assess the safety and efficacy of the CardioWest TAH. Copeland *et al*. [40] reported a 1-year survival rate of 70% among patients who received the TAH as a bridge to transplantation compared to 31% among the control patients. After transplantation, the 1- and 5-year survival rates were 86% and 64% respectively.

The AbioCor Implantable Replacement Heart (ABIOMED Inc., Danvers, MA) (Figure 15.12) is the first totally implantable artificial heart. Because it fits inside the body without penetrating

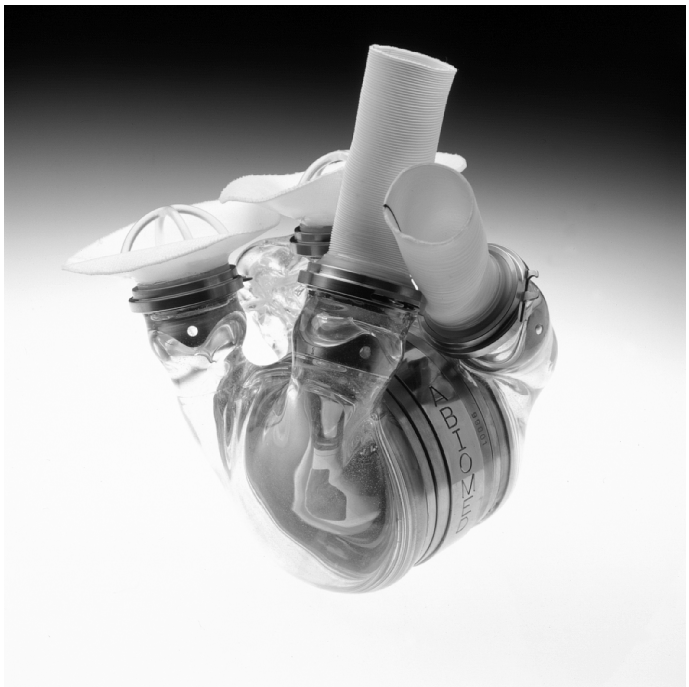

Figure 15.12 AbioCor Implantable Replacement Heart (ABIOMED Inc., Danvers, MA).

the skin, infection is avoided, and patients can maintain a relatively normal lifestyle. The AbioCor consists of an internal thoracic unit, which contains two artificial ventricles with their corresponding valves and a motor-driven hydraulic pumping system. The internal battery is recharged by a transcutaneous energy transmission (TET) system, or set of coils, one implanted internally and one placed externally overlying the internal coil, which transmits power across the skin without piercing it. This unique system gives the patient complete freedom from power base units and external battery packs, allowing them to move unrestrictedly. The initial clinical trial, which began in July 2001, enrolled 14 patients with end-stage biventricular failure who had exhausted all treatment options. Two patients died intra-operatively. Of the remaining 12 patients, 4 made excursions outside the hospital, and 2 were discharged to nearby facilities as a step toward discharge to home. These patients were able to go to restaurants, attend shows, sporting events, and religious services, and visit with family and friends at their homes. The longest-surviving patient was eventually discharged to home. The duration of support ranged from 56 to 512 days, with a cumulative duration exceeding 5.2 patient-years. On the basis of this experience, the AbioCor received a Humanitarian Device Exemption from the FDA in September 2006. The FDA now requires a Post Approval Study, which will consist of 25 patients in up to 10 US centers.

Axial flow pumps, a new generation of VADs, are currently in clinical trials for bridge to transplantation (BTT) and DT. This new generation of pumps is much smaller, approximately the size of a D-cell battery, and has few moving parts, so is much more silent (Figure 15.13). The continuous flow in axial flow pumps raises concern over the long-term effects of non-pulsatile flow. However, these effects are reduced when a patient's remaining heart function provides pulsatile flow and the axial pump only partially unloads the ventricle. In the event of device failure, the patient experiences hemodynamic perturbations similar to

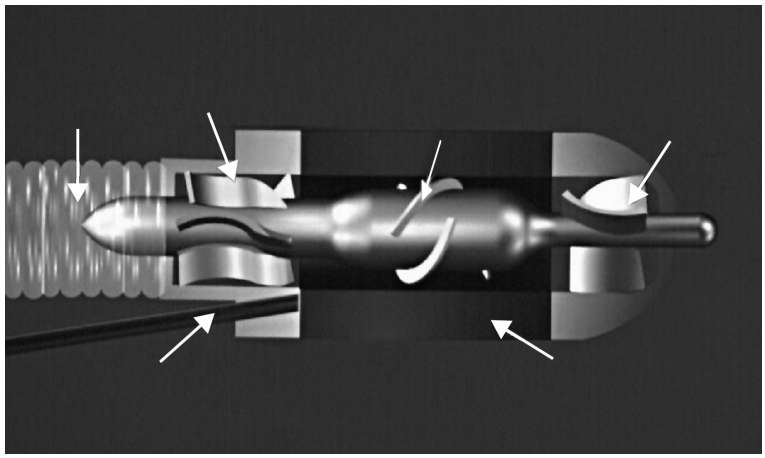

Figure 15.13 Axial flow pump (Courtesy of Texas Heart Institute, Houston, TX).

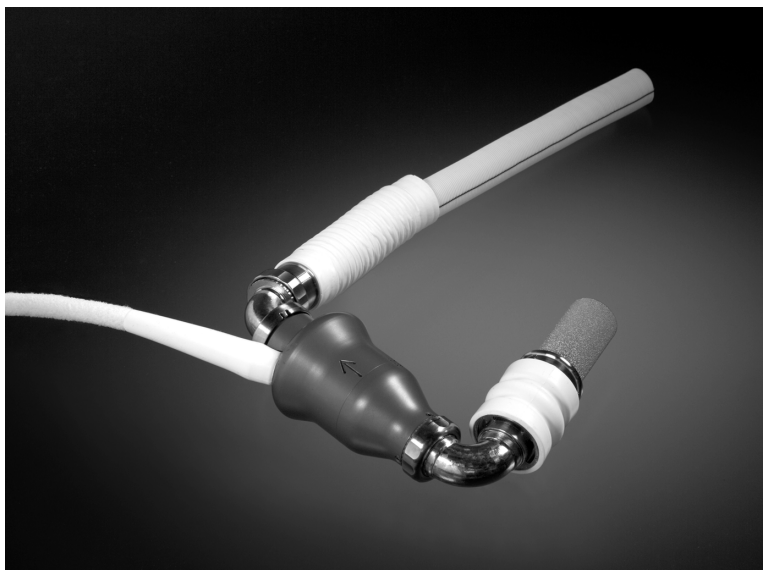

Figure 15.14 HeartMate® II LVAD (Thoratec Corporation, Pleasanton, CA).

those of acute aortic insufficiency, and emergent pump replacement is warranted. The Jarvik 2000 (Jarvik Heart® Inc., New York, NY) is the only intraventricularly positioned pump, and is fitted within the apex of the native left ventricle. Jarvik is currently enrolling up to 160 patients at 25 medical centers throughout the US in a pivotal trial for bridging to transplantation. The HeartMate II LVAD (Thoratec Corporation, Pleasanton, CA) (Figure 15.14) utilizes the TLC-II driver that is available for Thoratec VADs. The HeartMate Phase II clinical trial is evaluating bridge-to-transplant and DT patients in two separate arms.

Enrollment in the main bridge-to-transplant cohort has been completed for 133 patients at 26 sites, including 6-month follow-up. Seventy-five percent of the patients survived to transplantation, cardiac recovery, or ongoing support at 180 days while remaining transplant-eligible. Actuarial survival was 89% at 1 month, 75% at 6 months, and 68% at 12 months. During the support period (median 126 days, maximum 600 days), there were no mechanical blood-pump failures. Compared to the HeartMate I/VE experience, there was a significant decrease in adverse events: a 40% decrease in bleeding requiring surgery (0.78 vs 1.47 events/patient-year [pt-yr]), a 90% decrease in percutaneous lead infections (0.37 vs 3.49 events/pt-yr), and a 50% decrease in stroke (0.19 vs 0.44 events/pt-yr). These results were presented at the ACC meeting in March 2007, and a premarket approval application has been submitted to the FDA for use of the device as a bridge to transplantation.

Once a patient has been carefully selected, his or her status has been optimized preoperatively, and the most appropriate device has been selected, success rests in the hands of the multidisciplinary operating room team, including a cardiac surgeon, cardiac anesthesiologist with transesophageal echocardiography (TEE) skills and a perfusionist, as well as surgical nurses and an MCS team. Although thrombocytopenia is relatively common in end-stage heart failure patients, one must be particularly cognizant of heparin-induced thrombocytopenia (HIT) syndrome. Each VAD program should develop an institutional protocol for managing HIT patients with alternative anticoagulants, especially because of the lack of alternative FDA-approved anticoagulation regimens for use with CPB. Aprotinin dose testing should also be performed prior to making the incision for the VAD implant. If the patient is sensitized to aprotinin, ε-aminocaproic acid administration may be appropriate to assist with hemostasis. All blood products must be leukocyte depleted and filtered. Prophylactic antibiotics should be completed 30–60 minutes prior to incision.

On the patient's arrival in the operating room, an initial TEE should be closely inspected for a patent foramen ovale (PFO) or an atrial septal defect (ASD); valve dysfunction, namely aortic regurgitation, mitral stenosis, and tricuspid regurgitation; right ventricular (RV) function, and the presence of an intra-cardiac thrombus. A PFO or ASD requires closure at the time of VAD implantation to avoid paradoxical embolus if right-sided pressures increase post-operatively. Mitral stenosis or even-mild-to moderate aortic regurgitation necessitates correction to permit LVAD filling and prevent backflow into the left ventricle, respectively. A mechanical prosthetic aortic valve requires either removal and oversewing of the valve or replacement of the mechanical valve with a bioprosthesis. Hemodynamic management calls for avoidance of right ventricular (RV) distention, administration of pulmonary vasodilators, and initiation of inotropic support to improve RV function, as well as to avoid systemic hypotension. De-airing the pump and weaning from CPB are critical steps that require careful attention and collaboration among the VAD team members to achieve optimal outcomes. RV failure is common in patients who receive an LVAD only and, when refractory to pharmacologic support, mandates placement of a right VAD [41].

Post-operative management of the LVAD patient is in reality RV management (Figures 15.15 and 15.16) [42]. The LVAD may be set at a lower flow rate initially to avoid an intraventricular septal shift, over-distention of the RV, and subsequent RV failure. The goals of mechanical ventilation should be to minimize pulmonary vascular resistance by increasing pH, optimizing arterial oxygen tension (PaO_2), and decreasing arterial carbon dioxide tension ($PaCO_2$) in addition to limiting positive end-expiratory pressure (PEEP). Patients should be weaned from mechanical ventilation as quickly as possible, with an aggressive pulmonary toilet, to prevent development of pneumonia. Additional pulmonary vasodilators, including inhaled nitric oxide, intravenous (IV) milrinone, and IV prostaglandins may be required. Correction of any coagulation derangements and notification to the cardiac surgeon when LVAD pocket drainage or chest tube drainage

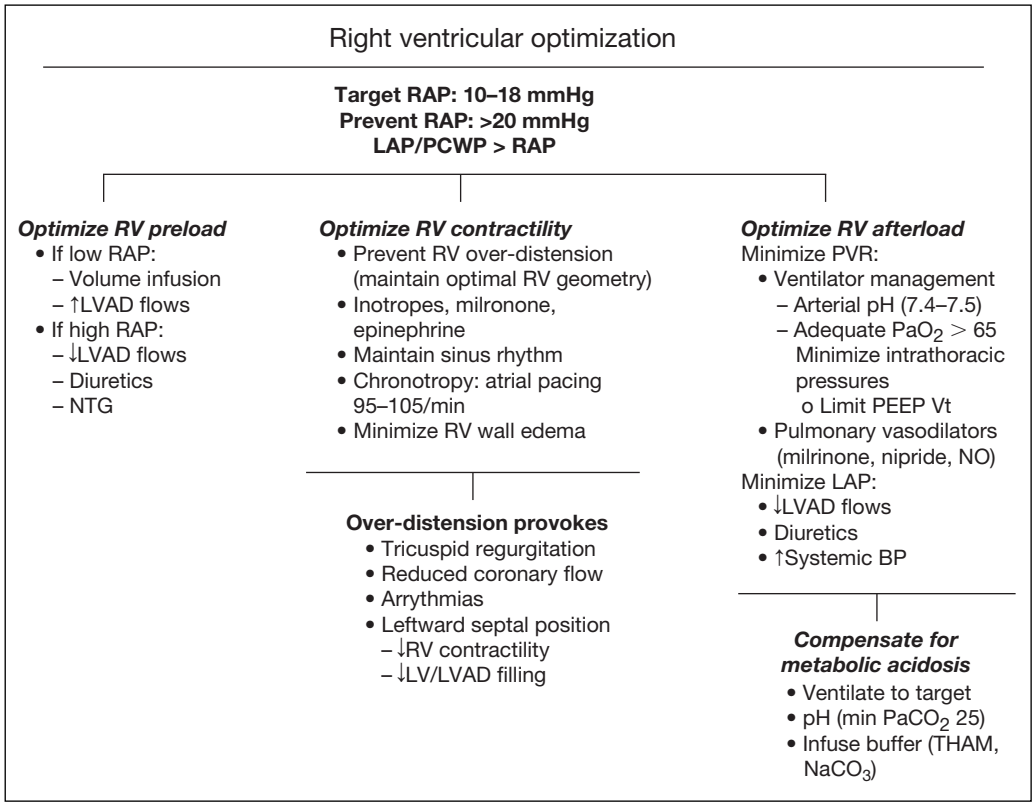

Figure 15.15 Right ventricular optimization. Adopted with permission from [42]. BP = blood pressure; LAP = left atrial pressure; LV = left ventricular; LVAD = left ventricular assist device; $NaCO_3$ = sodium carbonate; NO = nitrous oxide; NTG = nitroglycerin; PaO_2 = arterial oxygen tension; $PaCO_2$ = arterial carbon dioxide tension; PCWP = pulmonary capillary wedge pressure; PEEP = positive end-expiratory pressure; PVR = peripheral vascular resistance; RAP = right atrial pressure; RV = right ventricular; THAM = tromethamine; tris[hydroxymethyl]-aminomethane.

is >400 ml/h prevents excessive blood product administration. Arrhythmias may be treated pharmacologically or by cardioversion once the VAD is disconnected from the power source. Hypotension should alert the intensivist to possible RV failure, cardiac tamponade, SIRS, adrenal insufficiency, or LVAD dysfunction. Acidosis may cause pulmonary vasoconstriction and render inotropes ineffective and should therefore be corrected. Renal failure requires aggressive management with pharmacologic therapy or continuous veno–veno hemofiltration to avoid over-distention of the right ventricle and hypoxia. Agitation, delirium, and ICU psychosis, as well as adverse effects of sedatives and analgesics, can lead to neurologic dysfunction. These conditions are usually transient and will resolve once the patient's general condition has improved. The prophylactic antibiotic regimen should be completed and enteral nutritional support initiated as quickly as possible to promote wound healing and avoid infectious complications. Strict adherence to sterile technique with each dressing change and continual use of the immobilizer belt will dramatically reduce the risk of a drive-line infection. Either intensivists or cardiologists with expertise in MCS who can provide comprehensive detailed care in the ICU will greatly enhance the VAD patient's success post-operatively [42].

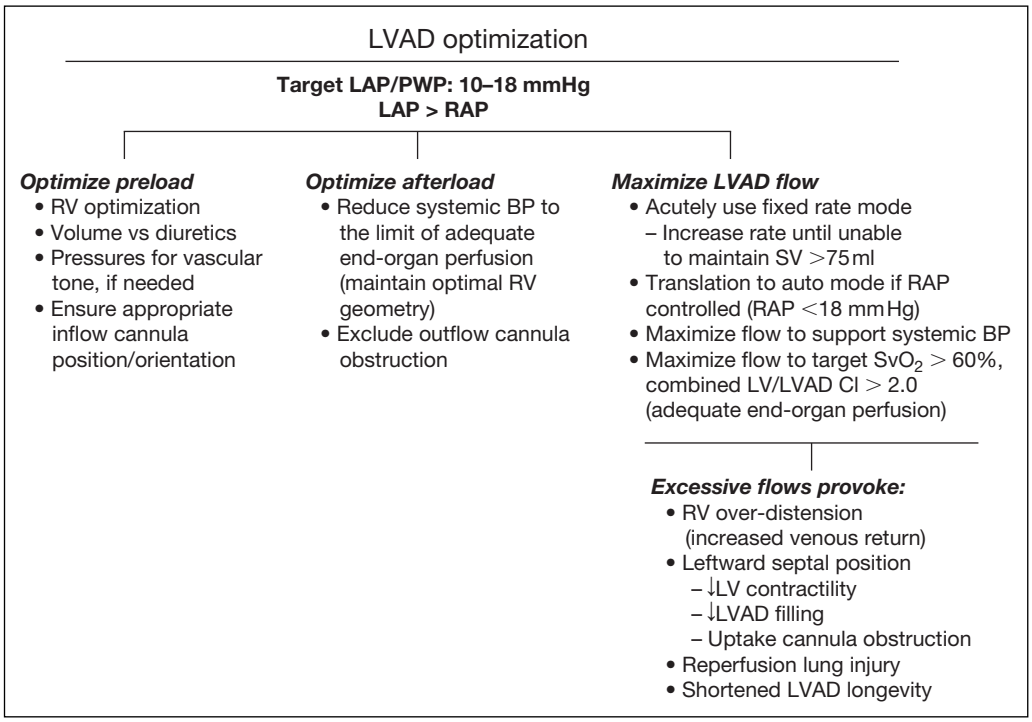

Figure 15.16 LAVD optimization. Adapted with permission from [42]. BP = blood pressure; CI = cardiac index; LAP = left atrial pressure; LV = left ventricular; LVAD = left ventricular assist device; RAP = right atrial pressure; RV = right ventricular; SV = stroke volume; SvO_2 = mixed venous oxygen saturation.

Optimal discharge planning begins at the initial evaluation of a patient for VAD support with a thorough assessment of the patient's psychosocial support system. The principal driver of success is a dedicated VAD coordinator who takes charge of the education of the patient and the patient's family support system. Facilitating discharge into the community of VAD patients involves the coordination of local physicians, emergency response teams, and community resources, and the management of ancillary equipment [43].

Since establishment of the Total Artificial Heart Program in 1964, MCS has had a tumultuous but progressive course. FDA-approved devices for bridging patients to recovery or transplantation, and for permanent therapy have become an integral part of the therapeutic armamentarium for end-stage heart failure. Devices are now available for support of the left or right ventricle, or for complete replacement of both ventricles. Systems can be implanted or inserted in a paracorporeal position to provide life-saving therapy to patients with diverse body sizes. The future holds much promise with improvements in patient selection, patient management, device durability, and miniaturization (Figure 15.17). Cellular-based therapy to augment reverse remodeling as an adjunct in restoring hemodynamic function with MCS, offers a new perspective in the advancing field of comprehensive treatment solutions for heart failure. With the melding of biology and technology, mechanical device therapy heralds the dawn of a new and exciting era in the treatment of end-stage heart failure.

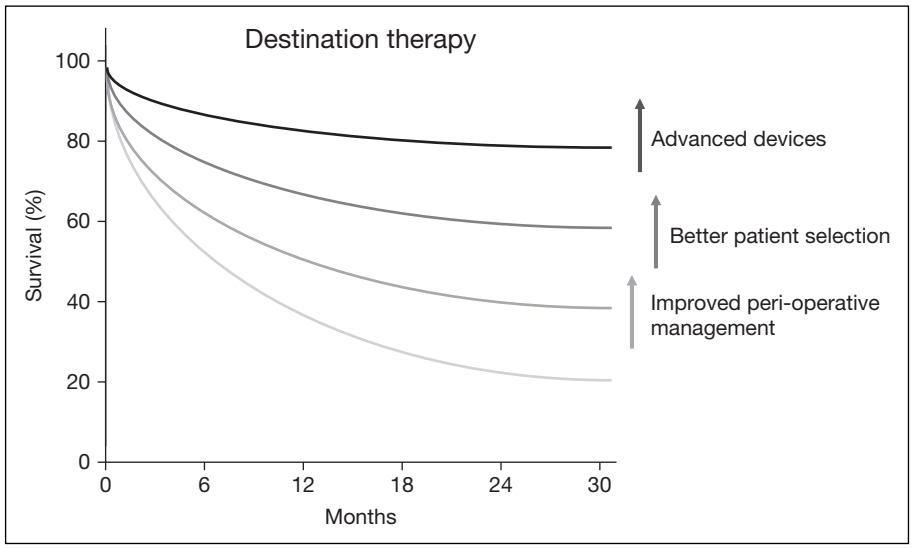

Figure 15.17 The effect of improvements in patient selection, patient management, device durability, and miniaturization on survival. Courtesy of James Long, MD, PhD. Latter Day Saints Hospital, Salt Lake City, UT.

SUMMARY

What is the role of ventricular replacement therapy for end-stage heart failure?

- Mechanical devices are available to support heart failure patients for three major indications:
  - Bridge to recovery.
  - Bridge to transplantation.
  - DT.
  - Appropriate patient selection is paramount in achieving successful outcomes with VAD placement.
  - Device selection is tailored by the expertise of the institution and the specific needs of the individual patient.
  - A multidisciplinary approach to pre-operative optimization and peri-operative care by a dedicated VAD team has improved outcomes dramatically.
  - Advances in device reliability, durability, and miniaturization will increase the number of patients who may benefit from MCS.

Therapeutic strategies for optimizing success with MCS include:

- Recognizing hemodynamics in the acute heart failure patient that warrant MCS.
- Identifying chronic heart failure patients who are candidates for DT.
- Refering early to an implanting center before the development of end-organ dysfunction.
- Maintaining open communication between referral centers and implanting centers to facilitate early transfer for MCS and early return of patients to their communities.

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