

Circulatory Assist Devices 2000: An Update

Mechanical circulatory assist devices have been used in clinical practice as a bridge to transplantation since the late 1960s. In 1982, the first totally artificial heart designated as permanent therapy was implanted, but relatively few totally artificial hearts are implanted today. In the last several years, there has been a shift toward the use of left ventricular assist devices as a bridge to cardiac transplantation. Likewise, there is increasing interest in the use of ventricular assist devices as a bridge to recovery for patients with myocarditis, dilated cardiomyopathy, and following myocardial infarction or cardiomyotomy. This review presents basic information on the present use of these devices as they relate to transplantation and recovery, and as permanent therapy. Individual devices will briefly be described, as will indications for, and timing of, implantation. Other related issues, such as right heart failure, pulmonary hypertension, arrhythmias, anticoagulation, and infections, will be addressed. In closing, the future of mechanical circulatory devices will be discussed.

(CHF. 2000;6:259-271) ©2000 by CHF, Inc.

*David B.S. Dyke, MD;¹ Francis D. Pagani, MD;²
Keith D. Aaronson, MD¹*

*From the Division of Cardiology¹ and the Section of
Cardiac Surgery,² University of Michigan Health
System, Ann Arbor, MI*

Address for correspondence/reprint requests:

*David B. S. Dyke, MD, Lecturer, Division of Cardiology,
Department of Internal Medicine, 1500 E. Medical
Center Drive, Ann Arbor, MI 48109*

Manuscript received May 22, 2000;

accepted July 10, 2000

History

The concept of replacing the failing human heart with a mechanical assist device dates back at least several hundred years. Early prototypes of ventricular assist devices began to emerge in the late 1800s and early 1900s. In 1928, H.H. Dale and E.H.J. Schuster developed the first diaphragm perfusion pump¹ and in 1934 Michael DeBakey developed the roller pump.² In 1935, a combined pump oxygenator was designed by Charles Lindbergh and Alexis Carrel in response to the illness of Lindbergh's sister-in-law, who suffered from valvular heart disease.³

The modern era of cardiac surgery began in 1952 with the first clinical use of a form of total mechanical cardiac assist, the heart-lung machine, designed by John Gibbon.⁴ Shortly thereafter, a totally artificial heart (TAH) developed by Drs. Willem Kolff and Tetsuzo Akutsu sustained a dog for 90 minutes.⁵ In 1967, Dr. Adrian Kantrowitz described the first use of an intra-aortic balloon pump,⁶ which to this day is the most widely used form of mechanical cardiac assist.

Denton Cooley performed the first human implant of a totally artificial heart in 1969.⁷ The device, designed by Domingo Liotta, successfully supported a patient for 64 hours until a donor heart was located. Totally artificial hearts have been used since that time as bridges to transplantation. To date, the most well publicized use of an artificial heart occurred in 1982 when Dr. William DeVries implanted a Jarvik-7 TAH into Dr. Barney Clark, a 61-year-old dentist who suffered from end stage cardiomyopathy.⁸ The patient's age and degree of pulmonary hypertension were contraindications to cardiac transplantation, and the device was implanted as a means of permanent therapy. Dr. Clark survived for 112 days before ultimately succumbing to sepsis and multisystem organ failure. Several more permanent implantations were performed, with disappointing results, and the device was relegated to use as a bridge to transplantation.

By 1985, multicenter trials to evaluate the use of left ventricular assist devices (LVAD) as a bridge to transplantation demonstrated promising results, and by 1994 the FDA had approved the use of a

LVAD for this indication.⁹ Although TAHs are still used clinically, LVADs, or more accurately, left ventricular assist systems (LVAS), are now the implantable devices most commonly used. With the initiation of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial,¹⁰ a comparison of the use of the TCI HeartMate LVAS vs. the best medical therapy for patients with severe heart failure, we once again turn toward the use of these devices as permanent, or destination, therapy.

Indications and Timing

In broad terms, indications for use of an assist device include failure to wean from cardiopulmonary bypass, inability to safely bridge a patient to transplant using standard medical and surgical therapies, cardiogenic shock in both transplant and non-transplant candidates, and life-threatening arrhythmias not amenable to medical or surgical therapy. The threshold for placing an assist device is related to the comfort level and experience of the cardiovascular surgeon and cardiologist, the types of assist devices at their disposal, and the local standard of care. Specific guidelines are listed in the Table. At our institution, criteria for placement of an assist device are not absolute, and the choice to proceed is individualized to the patient. For example, a patient with a cardiac index of 1.8 L/min/m² who has relatively good blood pressure, has no end organ dysfunction, and is reasonably well perfused might not benefit from implantation of a LVAD. In comparison, a patient with a cardiac index of 1.8 L/min/m², whose blood pressure is only 75/62 and serum sodium is 125, is likely to benefit from LVAD implantation.

While many patients with end stage heart disease have evidence of ongoing end organ dysfunction, implantation of a ventricular assist device is not contraindicated, provided that the dysfunction is not severe, or that it is believed to be reversible. For patients in whom the device is used as a bridge to transplantation, exclusion criteria are similar to the criteria used for transplant candidacy, with a few notable additions. For most devices, there is a patient size limit. For example, it is difficult to implant a Novacor[®] or HeartMate[®] if the body surface area of the patient is less than 1.5 m², or a CardioWest[®] TAH if the body surface area is <1.7 m². These general guidelines are somewhat dependent on the body habitus of the patient as well.

Severe coagulopathy poses a substantial surgical challenge, and is a strong relative if not absolute contraindication to implantation of most forms of

TABLE. INDICATIONS FOR THE INITIATION OF A MECHANICAL CIRCULATORY ASSIST DEVICE

AS A BRIDGE TO TRANSPLANT MUST MEET CRITERIA FOR TRANSPLANTATION
<ul style="list-style-type: none"> • Hemodynamic criteria: <ul style="list-style-type: none"> • Cardiac index <2.0 despite optimal inotropic therapy • Inability to maintain adequate SBP • PCWP >20 • Reversible neurologic dysfunction secondary to low flow • Reversible renal dysfunction secondary to low flow • Inability to maintain salt/water homeostasis despite diuretics and inotropic therapy • Inability to wean from ventilator secondary to persistent pulmonary edema • Inability to wean from IABP • Malignant, uncontrollable arrhythmias • Life-threatening coronary anatomy not amenable to percutaneous or surgical correction
OTHER INDICATIONS
<ul style="list-style-type: none"> • Failure to wean from CPB—postcardiotomy syndrome • As a bridge to ventricular recovery (example: acute myocarditis) • REMATCH candidate¹⁰
<p>PCWP=pulmonary capillary wedge pressure; SBP=systolic blood pressure; IABP=intra-aortic balloon pump; CPB=cardiopulmonary bypass.</p>

assist devices. Likewise, severe hepatic dysfunction is felt to be a contraindication to LVAD implantation, largely because of the resultant uncontrollable coagulopathy. In one series, preoperative hepatic dysfunction was the most consistent predictor of poor outcome.¹¹ We have used percutaneously placed extracorporeal membrane oxygenation (ECMO), more accurately known as extracorporeal life support (ECLS), to effect rapid and complete venous unloading, improve systemic perfusion, and optimize oxygen delivery, with the result of improvement in congestive hepatopathy and coagulopathy. With this strategy, the rate of LVAD survival after initial ECLS support of very high risk patients is not significantly different from the survival rate after LVAD placement alone in lower risk patients.¹² This strategy is also cost-effective because LVAD implantation, an expensive form of support, is not performed in those who do not survive the initial ECLS, which is a substantially less expensive option.

Profound or even complete renal dysfunction, although a risk factor for poor outcome,¹³ can be managed with traditional renal replacement therapy (continuous veno-venous hemofiltration [CVVH], continuous veno-venous hemofiltration with he-

modialysis [CVVH-D], or hemodialysis). In the setting of reversible renal dysfunction (such as acute tubular necrosis), substantial renal function usually returns within days to weeks after adequate perfusion is established by an assist device.

Appropriate timing for placement of a LVAD must be individualized to the patient. The window of opportunity is frequently narrow. The rule is to avoid implantation of a LVAD if it appears that standard medical therapy (for example, inotropes, diuretics, or implantable defibrillators) can safely bridge a patient to transplant. This assumes that during the waiting time for a donor organ, the patient can be active and mobile enough that adequate nutritional status, muscle mass, and strength are maintained, as severely debilitated patients have a much higher post-transplant mortality. If a reasonably appropriate physiology cannot be maintained, implantation of a LVAD is warranted.¹⁴ Implantation of a LVAD results in normalization of end organ function, which facilitates recovery to a healthier state than that prior to transplantation. If implantation is delayed for too long, profound end organ dysfunction can render a patient too ill to survive the implantation procedure. A risk factor selection scale based on easy-to-obtain clinical and laboratory data has been developed to help identify patients at high risk for LVAD postoperative death.¹⁵ In cases where risk is determined to be prohibitively high secondary to physiologic derangements, utilizing other means of ventricular support can help bridge the patient to a physiologic state compatible with LVAD implant survival.¹² Intra-aortic balloon counterpulsation, ECLS, and some of the extracorporeal devices can be extremely helpful in these situations.

We would like to think that economics should not play a role in deciding the most appropriate therapy for a patient. However, with the high cost of chronic intensive care, we are forced to consider the economics carefully. Despite the fact that an implantable LVAS is very costly, most of the cost is up front. Many of these patients can ultimately be discharged from the hospital to live at home, with minimal further cost.^{16,17} On the other hand, a single prolonged hospital admission, multiple hospital admissions, or home inotropic support, might in fact be even more costly.¹⁸ Consider the patient who is likely to be chronically hospitalized, but is unlikely to be transplanted within a short period of time because of body size, blood type, or panel reactive antibody status. In this patient, utilization of a LVAS would be a clinically and economically sound decision.

Devices Most Commonly Used in the U.S.

There are many forms of mechanical circulatory assist devices. A few are available only at tertiary or transplant centers, but many are available at hospitals that have either a catheterization laboratory or cardiac surgery capability. Approximately 35% of our LVAS patients are placed on some form of ventricular or circulatory support prior to transfer to our institution. Our recent success with LVADs and transplantation is a tribute to other physicians' ability to identify, triage, and appropriately manage patients with profound cardiac disease. With this in mind, we feel that it is appropriate to review all forms of mechanical circulatory assist devices so that this practice might continue.

Intra-Aortic Balloon Counterpulsation. This mode of ventricular assist is the most widely used form of mechanical ventricular support. Any form of left ventricular systolic dysfunction can be supported by the use of an intra-aortic balloon pump (IABP). An IABP can be used as a short-term bridge to recovery or transplant. One of the advantages of an IABP is that the device is reasonably portable, allowing hospital-to-hospital transfer without interruption of therapy. The major limitation is the relatively limited degree of support achieved with an IABP as compared to an implantable LVAD. Under optimal conditions, an IABP can increase cardiac index by only 15%–30%.

The IABP is usually emplaced percutaneously (occasionally by cut-down) via the femoral artery. Insertion can be performed in a cardiac catheterization laboratory, an operating room, and by skilled hands, at the bedside. The mechanism of action is dual. During diastole, balloon inflation augments aortic arterial pressure, with a resulting improvement in coronary perfusion. During systole, balloon deflation causes significant afterload reduction. The end result is improved myocardial and systemic oxygen delivery, decreased myocardial workload, and improved mean arterial pressure.

Contraindications to use of an IABP include severe aorto-ilio-femoral disease, aortic insufficiency, and aortic dissection. Risks include infection, bleeding, vascular trauma, embolization with loss of limb or end organ ischemia, and other difficulties caused by the immobilization required during support. The risk increases in proportion to duration of support, and because of this, an IABP is not the assist device of choice for long-term support. Systemic anticoagulation with heparin is generally required for prolonged use.

Extracorporeal Life Support (ECLS/ECMO).

These devices usually employ either roller pumps or centrifugal pumps in combination with a membrane oxygenator. The simplest form of this type of support is the heart-lung or cardiopulmonary bypass (CPB) machine, which can be used as a short-term bridge to a more permanent form of support. Long-term types of ECLS have largely been used in neonates and adults with acute respiratory distress syndrome. Although a few adult patients have been bridged to transplant with ECLS, the complications that occur with relatively brief support preclude its use for long-term ventricular support. It has been used as an effective short-term bridge to cardiac recovery. At other institutions¹³ as well as our own,¹² the indications for ECLS has been extended to cardiac patients with profound end organ dysfunction as a bridge to LVAD implantation.

Advantages of this type of system include percutaneous cannulation, full oxygenation as well as perfusion, and weaning capabilities. It can completely unload the venous system, allowing for resolution of congestive hepatopathy and nephropathy. Various forms of dialysis can be added in-line. Atrial septostomy should be performed by an experienced catheterization laboratory during ECLS support in the case of incomplete left atrial/ventricular unloading, in order to prevent pulmonary hemorrhage.¹⁹ At our institution, ECLS has been used successfully to provide temporary right ventricular assist (RVA[D]) after implantation of a LVAD, and is our RVAD of choice. We have used ECLS to treat severe pulmonary capillary leak syndrome secondary to a protamine reaction during LVAD implantation, and also in a similar situation (related to OKT3-induced cytokine release syndrome) after cardiac transplantation. Biventricular support can be achieved through venoarterial cannulation. It can be quickly implemented in cardiac arrest situations, particularly in the case of severe, uncontrollable ventricular arrhythmias.

An additional advantage to ECLS is that it is portable (our ECLS team routinely travels to outlying hospitals where ECLS is initiated, and the patient is transported to our institution by ground or air). Many cardiac catheterization laboratories have percutaneous cardiopulmonary bypass support (PCPS or CPS) capability, which is essentially a scaled down form of ECLS used for short-term support during high risk interventions. PCPS can be utilized to maintain a patient until arrival of the ECLS team. Switching over to ECLS from PCPS requires only up-sizing of the previously placed percutaneous lines.

Disadvantages and risks include the need for full anticoagulation with heparin, patient immobility,

infection, hemolysis, and the potential for embolization. Although ECLS is portable in our state, many regions do not have access to ECLS.

Centrifugal Pumps (Sarns Delphin® and Biomedicus® pumps).

These devices (CPs) are commonly used as the pump in cardiopulmonary bypass circuits. They are non-pulsatile devices that use centrifugal force to draw in and propel blood via inflow and outflow cannulae that enter the body through subcostal incisions. CPs can be used for uni- or biventricular support, can be implanted at any cardiac surgery center, are inexpensive, and are portable for patient transfer. They are best used for short periods of support (hours to days), hemolysis being the rate-limiting factor. These devices are frequently used in combination with intra-aortic counterpulsation. Systemic heparinization is required. Bedside operation requires the presence of a perfusionist.

ABIOMED BVS 5000® (ABIOMED, Inc., Danvers, MA).

This system is specifically designed as a form of ventricular support. It consists of an external pneumatic drive console, single-use extracorporeal blood pumps, and cannulae that enter the body through subcostal incisions. It can be configured as a RVAD, a LVAD, or a BiVAD, depending on the needs of the patient. The atria are the usual sites of inflow cannulation; however, left ventricular apical and right ventricular free wall cannulation are occasionally used. The great vessels are the usual sites for outflow cannulation, although transpulmonic valve cannulation for pulmonary outflow is occasionally used. Some surgeons have used a left mini-thoracotomy approach for less invasive cannulation. The design of the blood pump is unique. Blood flows via gravity drainage into the device inflow bladder, which functions as the atria of the device. Blood then passively flows across a trileaflet polyurethane inflow valve into the outflow bladder, which acts as the ventricle of the device. When this bladder fills, the console sends a pulse of compressed air into the gap between the surrounding plastic casing and the bladder. The resulting increase in pressure, which is transmitted to the blood column within the bladder, causes device "ventricular systole." Pulsatile blood flow is delivered to the patient through a second trileaflet valve and outflow cannula, with flows of up to 6 L/min. The console is simple to use, and relatively little monitoring is needed. It is FDA-approved as a bridge to any form of myocardial recovery, but is frequently used as a short- to medium-term bridge to a long-term ventricular assist device or trans-

plant. It can be implanted at any center that has cardiac surgery capability, and it is portable for center-to-center patient transfer. Systemic anticoagulation is required during support. In contrast to CPs, there is no need for a perfusionist; the device can be maintained by trained nursing staff. To date, the smallest patient successfully supported with this device is a 7 year-old boy with a body surface area of 0.85m². Although the system is bulky, patient ambulation is possible.

Thoratec® VAD System (Thoratec Laboratories Corporation, Pleasanton, CA). This device was initially designed by Dr. William Pierce and James Donachy at Pennsylvania State University. The pneumatically driven, pulsatile blood pump is designed for use as a RVAD, LVAD, or BiVAD, depending on the needs of the patient. The blood pump consists of a smooth, seamless polyurethane pumping chamber enclosed in a rigid case. Two mechanical valves maintain unidirectional flow. The stroke volume is 65 ml, with flow outputs that range from 1.3–7.2 L/min. The cannulation technique is variable, with inflow to the device through cannulation of the ventricles or atria and outflow from the device through cannulation of the great vessels. The blood pump(s) is paracorporeal, making it the most versatile system on the market. Because the device itself is outside the body, it can be used to support smaller patients, the smallest to date being a 17-kg patient with a BSA of 0.7 m². The drive console provides alternating pulses of vacuum and pressure to the device. It can be set in one of three different modes of operation, one of which allows for changes in device output, depending on the device inflow (venous return) of the patient. Although the console is quite large, a much smaller portable driver (the TLC-IITM) is currently in use in Europe and is under investigation in the U.S. The Thoratec VAD is the only device approved by the FDA for both bridge to transplant and postcardiotomy support. For the combined indications, this device has been used to support 912 patients to date. The longest duration of support with the Thoratec device is 515 days; the patient, who received univentricular support, was successfully transplanted.

Use of this device requires systemic anticoagulation. Heparin is administered after surgical bleeding is controlled, and is generally changed to warfarin during long-term use. Use of this device is primarily restricted to tertiary/transplant centers, as it requires expertise and resources not available in community hospitals. Patients can be discharged from the hospital while being supported by this device.

HeartMate® IP-LVAS and VE-LVAS (Thermo Cardiosystems Inc., Woburn, MA). There are actually two different HeartMate LVAD systems. Both consist of an implantable blood pump, which comprises a titanium alloy housing that contains a pusher plate behind a flexible polyurethane diaphragm. The inflow cannula is attached to the left ventricular apex, and the outflow cannula is anastomosed to the ascending aorta. Porcine valves within each cannula maintain unidirectional blood flow. The device is implanted in the left upper quadrant, either within the abdominal cavity or in a preperitoneal pocket, depending on the preference and experience of the surgeon.

One of the unique features of this device is that all blood-contacting surfaces (except the cannulae) are textured to promote the formation of a tightly adherent biologic pseudo-neointima, which allows blood to contact only a biologic surface. The titanium half of the interior of the device is lined with sintered titanium microspheres. The polyurethane half of the interior is similarly irregular. As a result, this device boasts an extraordinarily low thromboembolic rate of 2%–4%.^{20,21} Systemic anticoagulation is not required, although daily aspirin is recommended.

The two devices differ in the way the pusher plate is activated. For the pneumatic model (IP-1000 LVAS), an external console pneumatically activates the pusher plate through a driveline that exits the body through a stab wound in the abdominal wall. In the Vented Electric model (VE LVAS), an electric motor is housed behind the pusher plate. The motor is coupled to the external controller and console through a driveline that exits the body through a stab wound in the abdominal wall. Because this device requires venting of air in the motor section of the device, the driveline also serves as a vent. Should a problem develop with the motor or other electric components of the device, the vent can be attached to a pneumatic console, and the device becomes a functional IP-LVAS.

Both devices can be operated in two different modes: fixed rate and automatic. In automatic mode, the cardiac output is determined by the device inflow (venous return) of the patient, allowing for increased flow during exercise. The IP-1000 LVAS can support flows of up to 11.7 L/min, and the VE LVAS up to 10 L/min. The external console of the IP-1000 LVAS is bulky, and despite the fact that these patients are quite mobile, they usually remain hospitalized because of the size of the external console. A smaller portable console, the HeartPak®, is currently undergoing clinical trials. The VE LVAS console is smaller than the pneumatic console, and this device can be operated with two small, wearable

battery packs, which allow for untethered mobility for 8 hours per battery pair. Many of these patients can be discharged to home with relatively normal mobility. They can participate in activities such as shopping, golf, and walking. Many can return to work. To date, 2095 HeartMate devices have been implanted worldwide. The longest duration of support thus far is 873 days.

Use of this device is limited to patients with a BSA of 1.5 m² or greater. Because it is a pure LVAD, it provides no direct right ventricular support. However, decompression of the left atrium usually results in a decrease in pulmonary artery pressure and right ventricular afterload.

Novacor® N100 LVAS. (The Edwards Life Sciences Division, Worldheart Corp., Oakland, CA). This device consists of a blood pump that is implanted into the left upper quadrant, either within the abdominal cavity or in a preperitoneal pocket. Inflow and outflow cannulae attach to the left ventricular apex and the ascending aorta, respectively. Bovine pericardial valves are located in the cannulae and provide for unidirectional blood flow. The pump comprises a seamless polyurethane sac with two opposing pusher plates that are activated by an electromagnetically driven solenoid. The mechanical failure rate of this system is extraordinarily low, and is one of the strong points of the device. An electric driveline/vent exits the body through a stab wound in the abdominal wall. The driveline connects to a small controller that connects to an external console. The device operates in one of three modes and, unlike the HeartMate, can be synchronized to the patient's electrocardiogram, allowing for filling of the device during cardiac systole. It can also be configured to operate in asynchronous mode, which maximizes output during exercise by adjusting the pump rate to device inflow (venous return). A maximum output of 10 L/min can be obtained in this mode. A third mode of operation is fixed rate. The portable controller with external battery pack allows for several hours of untethered mobility. Many of these patients can be discharged to home with relatively normal mobility. The longest duration of support thus far is greater than 3 years. To date, 1136 Novacor devices have been implanted worldwide.

The Novacor LVAS requires systemic anticoagulation. Like the HeartMate, it requires a BSA of at least 1.5 m² and does not provide right ventricular support.

CardioWest C-70® TAH (CardioWest Technologies, Inc., Tucson, AZ). This totally artificial heart, the descendant of the Jarvik-7, is still in use in

several centers in the U.S. and Europe. The pneumatically driven prosthetic ventricles are made of polyurethane. A four-layer polyurethane diaphragm separates the air and blood sides of each artificial ventricle. Two Medtronic-Hall valves (per ventricle) provide for unidirectional blood flow. The native ventricles are completely excised. The device is connected to the native atria by Dacron cuffs and to the great vessels by Dacron vascular prosthetic grafts via a quick-connect system consisting of coated, rigid polycarbonate segments. Pneumatic drivelines exit the body through two incisions in the anterior abdominal wall. The external console allows for adjustment of driveline pressure, systolic duration, and pump rate, providing a maximal output of 9 L/min. The console is bulky, but a smaller drive unit is under development. Stroke volume (70 cc with maximum fill) is preload-dependent, allowing for augmented device output during exercise.

The CardioWest TAH requires aggressive systemic anticoagulation with a combination of warfarin and antiplatelet agents. Implantation of this device is limited to patients with a BSA of 1.7 m². To date, 155 CardioWest devices have been implanted worldwide. In a world dominated, at present, by pure left ventricular assist devices, there are some scenarios (e.g., a primary intracardiac tumor) in which a TAH is the treatment of choice.

Special Considerations, Complications, and Monitoring

Drivelines and External Cannula Sites. All of the implantable devices listed above have drivelines designed to promote tissue ingrowth. The Thoratec and ABIOMED BVS 5000® transcutaneous blood cannulae also share this design. Dacron velour is the most commonly utilized material. The advantage of this type of design (in comparison with the skin buttons used in the original Jarvik-7 devices) include a reduced incidence of ascending driveline infections and better stability.

Right Heart Dysfunction. Right heart failure is a common cause of morbidity and mortality in this group of patients, particularly in those receiving univentricular left-sided assist devices. Failure of the right side to deliver blood across the pulmonary vascular bed can lead to low flow in a LVAD, with the potential for device thrombosis. Factors influencing postoperative right heart function include preoperative right heart function, severity of right coronary artery (RCA) distribution coronary disease (particularly in the extreme case of RV infarction), modulation of pulmonary vascular resistance by intraoperative blood

products and cytokines related to cardiopulmonary bypass, and myocardial preservation techniques employed during CPB. In general, the best defense is a good offense. If profound or irreversible right-sided dysfunction is anticipated, use of a TAH or BiVAD is indicated over use of a LVAD. If a LVAD is implanted (with the hope of eventual right-sided recovery), transient right-sided support using ECLS, an Abiomed RVAD, or Thoratec RVAD may be required. Practically speaking, many patients can eventually be weaned from right-sided support. It is estimated that 10%–20%²² of patients receiving LVADs will need at least transient right ventricular support (RVAD, ECLS, or nitric oxide).

Other measures that can be utilized to maximize right-sided function include judicious preload augmentation with fluids, minimization of pulmonary vascular resistance (see below), tricuspid repair if severe tricuspid regurgitation is present, use of inotropes, such as isoproterenol, milrinone, and dobutamine, and pacing for chronotropic insufficiency. Given the predilection for postoperative bleeding in this group of patients, a high index of suspicion for intrathoracic bleeding with focal right atrial or ventricular tamponade is warranted. In case of poor device fit or transient chest wall edema, delayed sternal closure may prevent right ventricular compression.

In some patients with LVADs, profound right heart dysfunction is not necessarily problematic. In the setting of low pulmonary vascular resistance and a minimally regurgitant tricuspid valve, the ability to develop Fontan-like physiology (passive flow across the pulmonary vascular bed) can allow for adequate right to left flow with only minimal to modest elevation in central venous pressure.

Pulmonary Hypertension. Although pulmonary artery pressures frequently decrease after complete unloading of the left chambers, some patients develop reactive pulmonary hypertension in the intraoperative or immediate postoperative period. This is frequently in addition to some degree of mild to moderate fixed pulmonary hypertension related to chronic heart failure or intrinsic lung disease. The pathophysiologic state of pulmonary hypertension can have a profound impact on right ventricular function, and ultimately left-sided filling and cardiac/device output.

Modulation of pulmonary vascular resistance frequently can be achieved with pharmacologic or ventilatory agents. Adequate pO_2 and maintenance of mild respiratory alkalosis are of fundamental importance. Inotropes, such as dobutamine, milrinone, and isoproterenol, act as pulmonary vasodilators. Intravenous nitrates and nitroprusside are useful as

long as systemic pressure is not compromised. In extreme cases, intraoperative placement of a left atrial line may allow for administration of systemic circulation vasoconstrictor agents with concomitant use of vasodilators on the venous/pulmonary side.

Administration of inhaled nitric oxide into the ventilator circuit at a concentration of 20–40 ppm can be particularly useful in the setting of right heart failure associated with increased pulmonary vascular resistance.^{23,24} The local action of this agent allows for maximal pulmonary vasodilatation with virtually no effects on systemic pressures. It is also particularly helpful in managing post-transplant right-sided failure. Our experience with this inert gas has been positive, and results are sometimes quite impressive (as well as immediate). The FDA recently approved nitric oxide for the indication of neonatal acute respiratory distress syndrome. Use in adults is now off-label. Unfortunately, with market approval, the cost to obtain this agent has become prohibitively high for many institutions.

In patients without LVADs, nitric oxide is not safe to use in the setting of significantly elevated left ventricular end-diastolic pressure. If pulmonary vascular resistance is precipitously decreased in this setting, left ventricular and pulmonary venous pressures can acutely rise secondary to the increase in right-to-left flow. This can result in severe pulmonary edema.²⁵ It is, therefore, imperative that left ventricular filling pressure be normalized prior to initiation of nitric oxide in this setting. However, in the absence of mitral stenosis, a LVAD will effect nearly complete pulmonary venous unloading, making nitric oxide safe in this setting.

Arrhythmias. Ventricular decompression through use of a ventricular assist device can decrease myocardial ischemia and alleviate ventricular arrhythmias. Decreased atrial stretch can also reduce the frequency of atrial arrhythmias. Nonetheless, these patients are still at high risk for arrhythmias. Serious arrhythmias, such as ventricular tachycardia or fibrillation, can lead to hemodynamic instability in some patients. In other patients, malignant ventricular arrhythmias will have virtually no effect if Fontan-like right-to-left flow is adequate.²⁶ Right ventricular function and degree of pulmonary hypertension play a large role in the hemodynamic response of a patient to arrhythmia, particularly ventricular arrhythmia. Therefore, arrhythmias are less well tolerated in the first several days after device implantation because pulmonary vascular resistance is frequently elevated and right ventricular dysfunction is common in the immediate post-bypass physiologic state. Whether or not treatment for

an arrhythmia is indicated depends less upon the type of ventricular assist device than on the patient's response to the arrhythmia. In the presence of an isolated LVAD, atrial fibrillation with loss of atrioventricular mechanical coupling is usually well tolerated. If serious arrhythmias are likely to have profound consequences in a patient who is to be supported with a LVAD, a better choice would be support with a BiVAD or TAH.

Treatment with antiarrhythmic agents during ventricular assist support is relatively commonplace. Since many of these patients are able to tolerate severe ventricular arrhythmias, some physicians are more willing to use antiarrhythmic agents that are potentially proarrhythmic (class IA and IC agents). Amiodarone (a class III agent) is frequently used. Although it is one of the safest and most effective antiarrhythmics in this group of patients, it should be used judiciously. The very long half-life of the drug can cause severe chronotropic insufficiency in the donor heart sinus node following the transplant, for which implantation of a permanent pacemaker may be required.

Direct current cardioversion or defibrillation can be performed in the presence of most ventricular assist devices, but should not be performed (unless absolutely necessary) without full knowledge of the consequences to the electrical systems of the specific device being used. Temporary deactivation of the device is desirable in order to prevent damage to the electrical circuits. For this reason, internal cardioverter-defibrillators are frequently explanted at the time of LVAD implantation.

Given the side effect profile of most antiarrhythmic agents, the occasional patient will be better off with a sustained arrhythmia than with antiarrhythmic therapy. Most patients with ventricular assist devices are systemically anticoagulated, so the risk of arrhythmia-associated embolic events is generally low. The exception to this rule is the HeartMate device, since systemic anticoagulation is not required. In the presence of significant arrhythmias, heparin and/or warfarin should be added to the regimen of HeartMate patients.

Perioperative Hemodynamic Monitoring. As a consequence of the left ventricular (and therefore left atrial) unloading afforded by LVADs, monitoring of left atrial pressure is not clinically helpful, even in the immediate postoperative period. Device flow (a minimal estimate of actual forward cardiac output) is provided on all of the device consoles. Pulmonary artery catheters are therefore seldom needed. Because at least some degree of postoperative right heart dysfunction is present in many of

these patients, measurement of central venous pressure is helpful in order to maintain adequate right-sided filling pressures. Radial arterial lines are essential for the first day or two. In the optimal situation, indwelling catheters can be removed within 24–48 hours, which aids in preventing secondary device infections.

Invasive hemodynamic monitoring with a pulmonary artery catheter can be very helpful in some situations in which device malfunction is suspected. At our institution, we recently witnessed two cases of LVAD inflow valve incompetence. A significant regurgitant volume of blood between the device and the left ventricle caused both device consoles to display a device output that was inappropriately high. Measurement of the true cardiac output by the thermodilution technique, and of the actual pulmonary capillary occlusive pressure in the setting of the severe device regurgitation, allowed us to comfortably decide against exchanging the devices.

Infectious Complications. Due to the nature of this group of patients and the procedures required to sustain them, it is not surprising that infections are commonplace. Although many of these are routine infections, they are of particular concern because of the endovascular nature of the implanted device and the potential for seeding. Broad-spectrum antibiotic use is routine, particularly in the peri-implantation period. Because of this, many of the infections tend to involve resistant organisms (for example, methicillin-resistant staphylococcal species, vancomycin-resistant enterococci, and fungal species).

Rates of infection differ from center to center, and have been quoted to be from 23%–58%,^{27–29} with most large series reporting around 50%. A relatively high rate of fungal infections, usually candidal species, has been noted. It is unclear if any particular type of device is more prone to infectious complications.

Many of the infectious complications can be treated with local debridement, appropriate wound care, and intravenous and/or oral antibiotics. An example of this would be a local driveline infection, which is fairly common. Even though minor, if not managed appropriately, driveline infections can ascend and become a major device pocket infection or mediastinitis. Major device-related infections can require explantation and exchange for a new device, particularly if persistent bacteremia is present. Many patients have been transplanted in the presence of a LVAD infection. In fact, at some centers, urgent transplantation, using marginal donors if necessary, is the treatment of choice for device infections. Outcomes in perhaps the largest series

have been relatively favorable, with a survival rate to transplantation of 59%, as compared to 58% for patients without LVAD infections.³⁰ In this series, infections after transplantation were also not significantly different (35% vs. 28%). In rare cases, the best option is to explant the device and support the patient with medical therapy until the infection clears. In any case, infections will remain a problem at least until transcatheter energy transfer or internal battery systems replace traditional drivelines.

Given the fact that these devices are endovascular, care should be taken to ensure appropriate antibiotic prophylaxis during dental, airway, gastrointestinal, and urogenital procedures. At the present time no data exist concerning what type of antibiotic coverage should be used. At a minimum, AHA guidelines for bacterial endocarditis (SBE) prophylaxis³¹ for high risk patients (i.e., those with mechanical valves) should be followed.

Panel Reactive Antibodies. For patients awaiting transplant, panel reactive antibody (PRA) assays are used to identify those who have been presensitized to HLA antigens. A presensitized state is usually associated with prior organ transplant, blood product transfusion, or multiparity. It has been shown that patients with PRA levels of greater than 10% are more likely to have difficulties with early rejection.³² At many centers, it is typical to require a negative prospective lymphocytotoxic crossmatch prior to heart transplantation in the setting of a PRA of greater than 10%. The process of prospective crossmatching is time-consuming (which can jeopardize organ viability), and the wait time for a crossmatch-negative organ is typically significantly longer than if no crossmatch is required.

These issues are particularly pertinent to patients with ventricular assist devices, as there is a well known association between the presence of an assist device and elevated PRA levels. Why this occurs is not completely understood, but the association is likely to be a result of multiple factors. The use of blood products (particularly platelets) during implantation of these devices, the immunologic response of the patient to the biomaterials within the devices, and the length of exposure are all implicated. The development of a positive PRA after implantation of an assist device appears to be somewhat device-specific. Good data are sparse, but the literature suggests that short-term devices, such as the ABIOMED BVS 5000®, do not appear to stimulate this immunologic reaction. The long-term devices are more problematic.

The HeartMate devices appear to entail a higher incidence of elevated PRA levels than the other de-

vices. In one series of 40 HeartMate patients, PRA levels were found to be elevated in 45% of patients.³³ The rate appeared to drop with the addition of leukocyte filters used to decrease the perioperative antigenic load. In another series of HeartMate patients, avoidance of cellular blood products did not eliminate this problem.³⁴ It is likely that the textured surface design of the HeartMate devices either modulates the immune system directly or plays some role in modulating the immunologic response to foreign human leukocyte antigen loads. Other devices, such as the CardioWest and Novacor, appear to carry intermediate risk,³⁵ although only limited studies have been performed to examine this issue as it relates to these devices.

Clinical strategies for dealing with this problem include use of leukocyte filters for cellular blood products before, during, and after LVAD implantation, with avoidance of blood products if possible, and the use of drugs (aspirin or pentoxifylline) that may down-regulate the immune response to antigenic stimuli (by preventing activation of nuclear factor kappaB in particular). If an elevated PRA is noted, treatment options include the use of intravenous immunoglobulin, plasmapheresis, cytotoxic drugs, and mycophenolate mofetil. We have avoided the last three options because of the heightened risk of infection in the presence of an assist device. Once a significant positive PRA level is noted, it is likely that the waiting time for an organ (and device support time) will be significantly longer because of the need for a negative crossmatch. At our institution, we have noted that patients who develop a positive PRA after HeartMate implantation do not appear to have a higher incidence of rejection as compared to controls and that 2-year survival does not appear to be affected.³⁶ For patients who are presensitized prior to placement of an assist device, use of a less immunogenically active device may, however, be considered.

Thromboembolic Events. Thromboembolic (TE) rates have long been a weakness of mechanical circulatory devices. Rates of greater than 30% were commonly reported in the late 1980s.^{37,38} However, design changes and improved anticoagulation regimens appear to have significantly reduced the risk, and continual improvements make it difficult to quote exact TE rates for each device. Rates for most nontextured devices vary from 8%–35%.^{39,40} More recent reviews support TE rates of 14% for the ABIOMED BVS 5000® device (personal communication, Doug McNair), and 8% for the Thoratec device,⁴⁰ with fewer TEs noted with ventricular cannulation than with atrial cannulation. TE rates for the Novacor device range from 10%–35%,^{39,41}

although with recent cannula modifications this rate has been reduced to 5%⁴²–12%.⁴³ The addition of antiplatelet agents may also contribute to the lower rates observed recently.

TE events plagued the early years (and earlier incarnations) of the CardioWest device. More recent data demonstrate TE rates that range from 0%⁴⁴–26%.^{45,46} The recent improvements in TE rates with this device are probably related to more sophisticated anticoagulation regimens, which include warfarin, dipyridamole, pentoxifylline, aspirin, ticlopidine, and clopidogrel.

The HeartMate devices, with their textured surface technology, appear to consistently have lower TE rates. Most reports quote rates of 2%–4%.^{20,21}

Survival Rates. In a recent report⁴⁷ on the worldwide experience with the HeartMate devices, survival rates (to transplant or explant) were noted to be 71% for the IP-1000 LVAS and 58% for the VE LVAS, with rates of 73% and 63%, respectively, in the U.S.⁴⁷ Survival rates at the Cleveland Clinic have been as high as 76%.¹³ In our experience of 50 HeartMate implants, we have noted 80% survival to transplantation, with 97% survival to discharge after transplantation. In the Vented Electric bridge-to-transplant trial, the 1-year post-transplant survival was 84% (personal communication, Laura Damme).

Over one half of deaths during LVAD support with any of the assist devices occur within the first month of implantation. The HeartMate Registry data illustrate this well (similar data exist for the other LVADS). When these perioperative deaths are excluded, worldwide survival is 87% for the IP-1000 LVAS and 79% for the VE LVAS, with rates of 88% and 84%, respectively, in the U.S.⁴⁷ This highlights the importance of proper preoperative screening and the possible use of ECLS as a bridge to LVAD in selected high risk patients.

In a review of international experience with the CardioWest device, a survival to transplantation rate of 69%, and post-transplant survival to discharge rate of 92% were reported.⁴⁸ In a smaller series of U.S. recipients of this device, a survival rate of 93% was noted, with a post-transplant discharge to home rate of 96%.⁴⁶ In this series, survival to discharge for the control group of patients (no device) was only 39%.

In a recent review of the worldwide experience of the Novacor device, 58% of patients survived to transplant and 89% of these patients survived to discharge.⁴² In this review, 768 patients were implanted between 1984 and 1997. More recent data from a registry of 22 U.S. centers (129 patients)

demonstrate a survival to transplantation rate of 76%.⁴⁹ The University of Pittsburgh experience was a survival to transplant rate of 72%, with 84% of these patients surviving to discharge.⁴²

Worldwide results for the Thoratec VAD System (57% BiVAD, 40% LVAD, 3% RVAD) demonstrate a survival to transplant rate of 60%, with 86% of these patients surviving to discharge.⁵⁰ Overall post-transplant survival rates are comparable to the International Society for Heart and Lung Transplantation (ISHLT) Registry data. No relationship has been found between duration of VAD support and survival after transplantation.

From 1984 through 1996, a total of 1286 devices (Thoratec, Novacor, HeartMate, and CardioWest) were implanted worldwide as bridges to transplantation. Overall survival to transplant during that era was 60%, with 88.5% of those surviving to discharge. After transplantation, survival to discharge was similar for all devices, with rates between 81% and 92%.⁵¹

Survival rates vary greatly from study to study, and from center to center (even when the same device is compared). Device improvements, increased clinical expertise, better patient selection, and improved preventive strategies render data about survival rates quickly out of date and survival comparisons between devices limited.

Which Device Should I Use? Given the relatively small numbers of patients who require long-term mechanical support, the rapidly evolving technologies, and the large financial barriers, it is unlikely that a randomized trial of existing devices will ever be done. Also, it is likely that few, if any, cardiac surgery centers will be able to support the use of more than two or three types of devices. All present forms of mechanical assist devices have individual strengths and weaknesses, some of which are described above. None of the devices is clearly superior to the rest, and each fills a particular niche. Given these facts, the question of which devices to use can be best answered by the type of patient most likely to be seen at a given institution, the capabilities of that institution, and the comfort level of all involved medical staff with each device.

As a rule, it is necessary to have several different types of systems available. Each institution involved in long-term support of patients should have a device that will provide short-term support, such as ECLS, CP, or an ABIOMED BVS 5000®. For long-term support, a Novacor N100, a TCI Heartmate, a Thoratec, or a CardioWest should be available. In addition, there should also be a mechanism for

dealing with right ventricular failure. Options include nitric oxide (although on occasion this will not be adequate), and ECLS, CP, ABIOMED BVS 5000, Thoratec or CardioWest devices. Centers not committed to long-term support should have short-term support available, particularly if an active cardiology/cardiac surgery program is present.

Future of Ventricular Assist Devices and Artificial Hearts

It should be noted that the present use of ventricular assist systems does nothing to address the problem of a limited donor pool. In fact, it may actually make the problem worse. Many patients who receive mechanical ventricular support would not have survived to transplantation a few years ago. The number of donor hearts available per year leveled off several years ago, and in fact there has been a disturbing trend toward a decrease in the number of donors (United Network for Organ Sharing [UNOS] registry data presented at the International Society for Heart and Lung Transplantation annual meeting, April, 2000). Mechanical cardiac assist devices will likely provide at least a partial solution to this problem.

In the very near future, there is likely to be an increase in number of types of devices available to us. This is largely due to rapid improvement in the technology required for the design and testing of new devices. In addition, the existing technology will be applied to larger patient populations, and for broader indications.

A good example of the broader use of existing technology is the concept of implanting LVADs to bridge to recovery. Certain subsets of patients may benefit from long-term unloading of the left ventricle with ultimate device explant. Improvement in myocyte morphology,⁵² myocyte contractile properties, β adrenergic responsiveness,⁵³ the neurohormonal and cytokine profile,⁵⁴ and left ventricular contractility⁵² routinely have been demonstrated. It is possible that significant myocyte recovery might be achieved in some patients, to the extent that a transplant is no longer necessary.

A recent report from the German Heart Institute in Berlin⁵⁵ demonstrated successful device explantation after a recovery period in five of 17 patients with idiopathic dilated cardiomyopathy. Thus far, these results have not been reproduced at other institutions.⁵⁶ Reproducible prognostic indicators and physiologic markers for patients who are potential candidates for explantation have yet to be identified. Further discussion on this exciting topic is beyond the scope of this article.

Another good example of broader use of an existing technology is the Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure (REMATCH) trial.¹⁰ In this ongoing trial, patients with end stage congestive heart failure who are not transplant candidates (because of age or other factors) are randomly assigned to either best medical therapy or permanent (destination) implantation of a HeartMate VE-LVAS. If this trial demonstrates that quantity and quality of life are significantly improved at an acceptable cost, then LVAD implantation will become a viable option for tens of thousands of patients in this country alone. The Worldheart Corporation (formerly known as the Novacor Division, Baxter Health Care Co.) has recently received FDA approval for a feasibility study, the Investigation for Nontransplant Eligible Patients Who are Inotrope Dependant (INTrEPID), which involves the use of their device as a destination therapy in comparison to standard medical therapy (personal communication, Frank Beering).

As another example, Thoratec Laboratories is in the process of developing an implantable ventricular assist device, or IVAD.⁵⁰ The design of the pump is basically the same as that of the company's existing blood pump, with the advantage of having only one exiting drive line as opposed to two exiting blood cannulae. It will be significantly smaller than the Novacor or HeartMate devices, and therefore will benefit smaller patients.

As for new technology, the trend in the near future is for transcatheter energy transfer systems that will eliminate the need for drivelines. The first human implant of the LionHeart™ occurred on October 26, 1999 in Germany. The LionHeart LVAS, developed by Arrow International in collaboration with Pennsylvania State University, utilizes a transcatheter energy transfer system, implanted batteries, controller, and electrically powered blood pump equipped with two tilting-disk valves. The device is entirely implantable. A compliance chamber, placed in the left pleural space, allows for device venting. A subcutaneous access port allows for periodic percutaneous needle gas equilibration in order to maintain gas volume within the system. Energy is transferred via an external skin coil that is placed over the internal coil, and internal batteries allow for 20 minutes of untethered activity. The external battery pack allows for 2–3 hours of power for mobile operation away from the floor-based power charger. Because of the presence of mechanical valves, patients will require long-term systemic anticoagulation. This device has been designed as destination therapy, and not for bridge to transplant or recovery, and is intended for class IV patients who

are considered ineligible for heart transplantation. A clinical trial of this device in a total of 30 patients is ongoing in Europe. It is expected that the FDA will approve this device for clinical trials in the U.S. in the next few months.

Thoratec Laboratories is currently developing a muscle-powered ventricular assist device, or MVAD,⁵⁰ designed to be used as an alternative to transplantation. The device converts the mechanical energy of a stimulated latissimus dorsi into hydraulic energy that drives the VAD. It is designed to be completely internal and free of external drivelines.

ABIOMED, Inc. is in the process of developing a new TAH called the AbioCor™.⁵⁷ This device will incorporate two artificial ventricles, polyurethane valves, a motor-driven hydraulic pumping system, a transcutaneous energy transmission system, and an externally worn battery pack. It is being designed as an alternative to transplant. Clinical trials of this device, as well as the Penn State TAH (which will also utilize a transcutaneous energy transmission system) will likely begin within the next year or two.

Another technological advance that will be in clinical use very soon is the axial flow pump. Several groups are in the process of developing this type of device. The NASA/DeBakey VAD™ system, consists of a titanium inflow cannula that connects the pump to the apex of the left ventricle, a miniaturized axial flow pump, and a vascular graft outflow cannula that connects the pump to the ascending aorta. The device has a rotor speed of 10,000 rpm and can deliver 5 L/min. A driveline connects the device to an external controller system. This device is the first axial flow device used in humans.⁵⁸ Thus far it has been tested in approximately two dozen patients as a bridge to transplantation. At present, this device is under investigation in Europe.

The Jarvik-2000⁵⁹ device is a compact axial flow impeller blood pump that is inserted into the left ventricle through a sewing cuff anchored into the left ventricular apex. A Dacron outflow graft is anastomosed into the descending thoracic aorta. The device is 2.5 x 5.5 cm, weighs 85 g, and has a displacement volume of 25 ml (a pediatric version of the same pump is even smaller). It operates at speeds of 8000–12,000 rpm and can provide non-pulsatile blood flow of 8 L/min. There are no valves. Although it is designed as a LVAD, it is possible that it can be configured to function as a RVAD or BiVAD. A distinct advantage of this device is that it is quiet, unlike existing devices. The present incarnation of this device has a small driveline cable; however, a transcutaneous energy system will likely be available in the near future. Animal studies with this device have been promis-

ing. The first implantation of the Jarvik-2000 in a human occurred several weeks prior to the completion of this article.

Thermo Cardiosystems is currently developing a similar axial flow impeller device, the Nimbus/TCI device, also called the HeartMate II.²⁰ Clinical trials using this device in humans are scheduled to begin in the summer of 2000 in Israel. The Sun Medical/HIJ/Waseda/Pittsburgh axial flow pump is also under development. These new devices will broaden our patient population to include smaller adults as well as children.

Conclusion

As we enter the new millennium, our options for treating patients with end stage heart failure, surgical as well as medical, will continue to expand. Hundreds of thousands of patients will benefit from the future generations of devices that arise from our present-day cardiac assist technology.

REFERENCES

- 1 Dale HH, Schuster EHJ. A double perfusion pump. *J Physiol.* 1928;64:356–364.
- 2 DeBakey ME. A simple continuous flow blood transfusion instrument. *New Orleans Med Surg J.* 1934;87:386–389.
- 3 DeVries WC, Joyce LD. The artificial heart. *Clin Symposia.* 35(6):1–32.
- 4 Gibbon JH Jr. Application of a mechanical heart and lung apparatus to cardiac surgery. *Minn Med.* 1954;37:171–180.
- 5 Akutsu T, Kolff WJ. Permanent substitutes for valves and hearts. *Trans Am Soc Artif Intern Organs.* 1958;4:230–235.
- 6 Kantrowitz A, Tjonneland S, Freed PS, et al. Initial clinical experience with intraaortic balloon pumping in cardiogenic shock. *JAMA.* 1968;203(2):113–118.
- 7 Cooley DA, Liotta D, Hallman GL, et al. Orthotopic cardiac prosthesis for two-staged cardiac replacement. *Am J Cardiol.* 1969;24(5):723–730.
- 8 DeVries WC, Anderson JL, Joyce LD, et al. Clinical use of the total artificial heart. *N Engl J Med.* 1984;310(5):273–278.
- 9 Goldstein DJ, Oz MC, Rose EA. Implantable left ventricular assist devices. *N Engl J Med.* 1998;339(21):1522–1533.
- 10 Rose EA, Moskowitz AJ, Packer M, et al. The REMATCH trial: Rationale, design, and end points. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure. *Ann Thorac Surg.* 1999;67(3):723–730.
- 11 Reinhartz O, Farrar DJ, Hershon JH, et al. Importance of preoperative liver function as a predictor of survival in patients supported with Thoratec ventricular assist devices as a bridge to transplantation. *J Thorac Cardiovasc Surg.* 1998;116(4):633–640.
- 12 Pagani FD, Lynch W, Swaniker F, et al. Extracorporeal life support to left ventricular assist device bridge to heart transplant: A strategy to optimize survival and resource utilization. *Circulation.* 1999;100(suppl 19):II206–210.
- 13 McCarthy PM, Smedira NO, Vargo RL, et al. One hundred patients with the HeartMate left ventricular assist device: Evolving concepts and technology. *J Thorac Cardiovasc Surg.* 1998;115(4):904–912.
- 14 Frazier OH, Macris MP, Myers TJ, et al. Improved survival after extended bridge to cardiac transplantation. *Ann Thorac Surg.* 1994;57(6):1416–1422.
- 15 Oz MC, Goldstein DJ, Pepino P, et al. Screening scale predicts patients successfully receiving long-term implantable left ventricular assist devices. *Circulation.* 1995;92(suppl 9):II169–73.

- 16 Mehta SM, Aufiero TX, Pae WE Jr, et al. Mechanical ventricular assistance: An economical and effective means of treating end-stage heart disease. *Ann Thorac Surg.* 1995;60(2):284-290.
- 17 Morales DL, Catanese KA, Helman DN, et al. Six-year experience of caring for forty-four patients with a left ventricular assist device at home: Safe, economical, necessary. *J Thorac Cardiovasc Surg.* 2000;119(2):251-259.
- 18 Gelijns AC, Richards AF, Williams DL, et al. Evolving costs of long-term left ventricular assist device implantation. *Ann Thorac Surg.* 1997;64(5):1312-1319.
- 19 Mosucci M, Lynch W, Swaniker F, et al. Atrial balloon septostomy in the management and prevention of pulmonary hemorrhage in patients requiring extracorporeal life support. Extracorporeal Life Support Organization 9th annual meeting, Ann Arbor, MI; 1999.
- 20 Poirier VL. Worldwide experience with the TCI HeartMate system: Issues and future perspective. *Thorac Cardiovasc Surg.* 1999;47(suppl 2):316-320.
- 21 Rose EA, Levin HR, Oz MC, et al. Artificial circulatory support with textured interior surfaces: A counterintuitive approach to minimizing thromboembolism. *Circulation.* 1994;90(5 pt II):II87-91.
- 22 Arabia FA, Smith RG, Rose DS, et al. Success rates of long-term circulatory assist devices used currently for bridge to heart transplantation. *ASAIO J.* 1996;42(5):M542-546.
- 23 Argenziano M, Choudhri AF, Moazami N, et al. Randomized, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. *Ann Thorac Surg.* 1998;65(2):340-345.
- 24 Hare JM, Sherman SK, Body SC, et al. Influence of inhaled nitric oxide on systemic flow and ventricular filling pressure in patients receiving mechanical circulatory assistance (published erratum. *Circulation.* 1997;96(3):1065). *Circulation.* 1997;95(9):2250-2253.
- 25 Loh E, Stamler JS, Hare JM, et al. Cardiovascular effects of inhaled nitric oxide in patients with left ventricular dysfunction. *Circulation.* 1994;90(6):2780-2785.
- 26 Oz MC, Rose EA, Slater J, et al. Malignant ventricular arrhythmias are well tolerated in patients receiving long-term left ventricular assist devices. *J Am Coll Cardiol.* 1994;24(7):1688-1691.
- 27 Myers TJ, McGee MG, Zeluff BJ, et al. Frequency and significance of infections in patients receiving prolonged LVAD support. *ASAIO Trans.* 1991;37:M283-285.
- 28 Frazier OH, Duncan JM, Radovancevic B, et al. Successful bridge to heart transplantation with a new left ventricular assist device. *J Heart Lung Transplant.* 1992;11:530-537.
- 29 Kormos RL, Murali S, Dew A, et al. Chronic mechanical circulatory support: Rehabilitation, low morbidity, and superior survival. *Ann Thorac Surg.* 1994;57:51-58.
- 30 Argenziano M, Catanese KA, Moazami N, et al. The influence of infection on survival and successful transplantation in patients with left ventricular assist devices. *J Heart Lung Transplant.* 1997;16(8):822-831.
- 31 Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *Circulation.* 1997;96(1):358-366.
- 32 Lavee J, Kormos RL, Duquesnoy RJ, et al. Influence of panel-reactive antibody and lymphocytotoxic crossmatch on survival after heart transplantation. *J Heart Lung Transplant.* 1991;10(6):921-929.
- 33 Moazami N, Itescu S, Williams MR, et al. Platelet transfusions are associated with the development of anti-major histocompatibility complex class I antibodies in patients with left ventricular assist support. *J Heart Lung Transplant.* 1998;17(9):876-880.
- 34 Stringham JC, Bull DA, Fuller TC, et al. Avoidance of cellular blood product transfusions in LVAD recipients does not prevent HLA allosensitization. *J Heart Lung Transplant.* 1999;18(2):160-165.
- 35 Tsau PH, Arabia FA, Toporoff B, et al. Positive panel reactive antibody titers in patients bridged to transplantation with a mechanical assist device: Risk factors and treatment. *ASAIO J.* 1998;44(5):M634-637.
- 36 Pagani FD, Dyke DB, Wright S, et al. Development of anti-major histocompatibility complex class I or II antibodies following LVAD implant: Effects on subsequent allograft rejection and survival (abstract). *J Heart Lung Transplant.* 2000;19(1):57.
- 37 Icenogle TB, Smith RG, Cleavinger M, et al. Thromboembolic complications of the Symbion AVAD System. *Artificial Organs.* 1989;13(6):532-538.
- 38 Levinson MM, Smith RG, Cork RC, et al. Thromboembolic complications of the Jarvik-7 total artificial heart: Case report. *Artificial Organs.* 1986;10(3):236-244.
- 39 Wagner WR, Johnson PC, Kormos RL, et al. Evaluation of bioprosthetic valve-associated thrombus in ventricular assist device patients. *Circulation.* 1993;88(5 pt 1):2023-2029.
- 40 Farrar DJ, Hill JD. Univentricular and biventricular Thoratec VAD support as a bridge to transplantation. *Ann Thorac Surg.* 1993;55(1):276-282.
- 41 Kormos RL, Murali S, Dew MA, et al. Chronic mechanical circulatory support: Rehabilitation, low morbidity, and superior survival. *Ann Thorac Surg.* 1994;57(1):51-57.
- 42 Murali S. Mechanical circulatory support with the Novacor LVAS: World-wide clinical results. *Thorac Cardiovasc Surg.* 1999;47(suppl 2):321-325.
- 43 Ramasamy N, Wheelton D, Jansen P, et al. Reduction of embolic complications in left ventricular assist systems (LVAS) recipients: Impact of inflow conduit design (abstract). *J Heart Lung Transplant.* 2000;19(1):58.
- 44 Szefer J. Control and treatment of hemostasis in cardiovascular surgery. The experience of La Pitie Hospital with patients on total artificial heart. *Int J Artificial Organs.* 1995;18(10):633-648.
- 45 Johnson KE, Prieto M, Joyce LD, et al. Summary of the clinical use of the Symbion total artificial heart: A registry report. *J Heart Lung Transplant.* 1992;11(1pt1):103-116.
- 46 Copeland JG III, Arabia FA, Banchy ME, et al. The CardioWest total artificial heart bridge to transplantation: 1993 to 1996 national trial. *Ann Thorac Surg.* 1998;66(5):1662-1669.
- 47 HeartMate LVAS Clinical Results, January 2000. Data on file with Thermo Cardiosystems Inc.
- 48 Copeland JG, Arabia FA, Smith RG, et al. Arizona experience with CardioWest total artificial heart bridge to transplantation. *Ann Thorac Surg.* 1999;68(2):756-760.
- 49 Kormos RL, Ramasamy N, Sit S, et al, for the U.S. Multi-center Investigators. Bridge-to-transplant (BTT) experience with the Novacor Left Ventricular Assist System (LVAS): Results of a multicenter study. *J Heart Lung Transplant.* 1999;18(1):63.
- 50 Thoratec VAD System Clinical Monograph. January, 2000.
- 51 Arabia FA, Smith RG, Rose DS, et al. Success rates of long-term circulatory assist devices used currently for bridge to transplantation. *ASAIO J.* 1996;42(5):M542-546.
- 52 Frazier OH, Benedict CR, Radovancevic B, et al. Improved left ventricular function after chronic left ventricular unloading. *Ann Thorac Surg.* 1996;62(3):675-681.
- 53 Dipla K, Mattiello JA, Jeevanandam V, et al. Myocyte recovery after mechanical circulatory support in humans with end-stage heart failure. *Circulation.* 1998;97(23):2316-2322.
- 54 Delgado R III, Radovancevic B, Massin EK, et al. Neurohormonal changes after implantation of a left ventricular assist system. *ASAIO J.* 1998;44(4):299-302.
- 55 Muller J, Wallukat G, Weng YG, et al. Weaning from mechanical cardiac support in patients with idiopathic dilated cardiomyopathy. *Circulation.* 1997;96(2):542-549.
- 56 Mancini DM, Benjaminovitz A, Levin H, et al. Low incidence of myocardial recovery after left ventricular assist device implantation in patients with chronic heart failure. *Circulation.* 1998;98(22):2383-2389.
- 57 Abiomed Annual Report, 1998. Danvers, MA.
- 58 Wieselthaler GM, Schima H, Hiesmayr M, et al. First clinical experience with the DeBakey VAD continuous-axial-flow pump for bridge to transplantation. *Circulation.* 2000;101(4):356-359.
- 59 Westaby S, Katsumata T, Houel R, et al. Jarvik 2000 heart: Potential for bridge to myocyte recovery. *Circulation.* 1998;98(15):1568-1574.