

Review Article

*Medical Progress***IMPLANTABLE LEFT VENTRICULAR ASSIST DEVICES**DANIEL J. GOLDSTEIN, M.D., MEHMET C. OZ, M.D.,
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CONGESTIVE heart failure affects about 1 percent of adults in the United States¹ and is a contributing factor in over 250,000 deaths annually.² It is diagnosed in 400,000 Americans each year³ and is the primary diagnosis for over 900,000 hospitalizations per year.⁴

In 1990 the age-adjusted death rate from congestive heart failure was 106.4 per 100,000,⁵ more than that from breast cancer and the acquired immunodeficiency syndrome combined.^{6,7} The median survival after diagnosis is 1.7 years in men and 3.2 years in women, with a 5-year survival rate of less than 50 percent.⁸ Even though medical therapies have improved survival and the quality of life,^{9,10} recent estimates indicate that nearly 60,000 patients annually in the United States could benefit from heart transplantation or long-term mechanical support.¹¹

The introduction of cyclosporine in the 1980s¹² established heart transplantation as the most effective therapy for end-stage heart disease, including congestive heart failure, with 10-year survival rates after transplantation approaching 50 percent.¹³ The condition of an increasing number of patients deteriorates, however, to the point that they require continuous intravenous inotropic support until a suitable donor heart becomes available — and up to 30 percent die before that occurs.¹⁴ In 1996, 10.4 percent of patients awaiting heart transplantation died before receiving a heart.¹⁵ Efforts aimed at increasing the supply of donor organs¹⁶ — currently about 2500 hearts annually¹⁷ — have failed to ameliorate the shortage, underscoring the crucial need for alternatives to cardiac allotransplantation. Mechanical

support by means of ventricular assist devices is at present the most promising alternative.

VENTRICULAR ASSIST DEVICES

Ventricular assist devices are mechanical pumps that take over the function of the damaged ventricle and restore normal hemodynamics and end-organ blood flow. These devices are useful in two groups of patients. The first group consists of patients who require ventricular assistance to allow the heart to rest and recover its function. Under these circumstances, it is critical to obtain complete drainage of the ventricle in order to unload the ventricle, diminish myocardial work, and maximize subendocardial perfusion.¹⁸ Most often, these are patients with post-cardiotomy shock. The second group consists of patients with myocardial infarction, acute myocarditis, or end-stage heart disease who are not expected to recover adequate cardiac function and who require mechanical support as a bridge to transplantation.¹⁹⁻²²

The available ventricular assist devices include extracorporeal membrane oxygenation, univentricular and biventricular extracorporeal nonpulsatile devices, extracorporeal and implantable pulsatile devices, and the total artificial heart (Table 1). Although most of these devices require the patient to be connected to cumbersome extracorporeal drive systems, miniaturization of control and power-supply components has resulted in the development of wearable left ventricular assist devices. This latest generation of devices makes possible patients' rehabilitation, unrestricted mobility, discharge home, and return to work.²³ The increasing duration of implantation now raises the critical question of the suitability of implantable left ventricular assist devices for long-term use,²⁴ for which they may have some advantages over heart transplantation. These include the possibility of earlier intervention and rehabilitation and the avoidance of the risks associated with immunosuppression and of rejection. Most important, the devices could be produced in the quantities required to treat all the patients who might otherwise die before receiving a transplanted heart. This review will focus on the development of implantable left ventricular assist devices.

A HISTORICAL PERSPECTIVE

In 1964 the National Heart, Lung, and Blood Institute began to sponsor the development of mechanical devices for short- and long-term circulatory support, including a total artificial heart (Table 2).²⁵ Ten years later, support focused on the development of electrically powered, totally implantable devices,

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TABLE 1. CLINICALLY TESTED MECHANICAL PUMPS FOR CARDIAC SUPPORT.

PUMP TYPE*	ADVANTAGES	DISADVANTAGES	INDICATIONS
Extracorporeal nonpulsatile†	Simple cannulation, inexpensive, univentricular or biventricular, readily available, extensive clinical experience	Short-term support, requires continuous availability of trained bedside personnel, systemic anticoagulant therapy needed, bleeding and thromboembolism possible, patient necessarily bedridden, no potential for rehabilitation	Postcardiotomy ventricular dysfunction, neonatal respiratory failure (extracorporeal membrane oxygenation)
Extracorporeal pulsatile‡	Univentricular or biventricular	Short-term support, systemic anticoagulant therapy needed, patient usually bedridden, bleeding and thromboembolism possible, limited potential for rehabilitation	Postcardiotomy ventricular dysfunction, right-sided heart failure after left ventricular assist device implantation, bridge to transplantation
Implantable pulsatile§	Potential for outpatient and long-term support, excellent potential for rehabilitation	Expensive, univentricular support, abdominal placement required, infection possible, mechanical failure possible, bleeding and thromboembolism possible	Bridge to transplantation, bridge to recovery, potential long-term use
Total artificial heart¶	Biventricular support, orthotopic placement	Not FDA-approved, bleeding and thromboembolism possible, bulky external console, systemic anticoagulant therapy needed, infection possible, mechanical failure possible, expensive	Biventricular failure, bridge to transplantation

*The intraaortic balloon pump is not included here, because it does not produce its own stroke volume.

†Centrifugal-flow pumps and extracorporeal membrane oxygenation are included in this category.

‡The Pierce–Donachy device (Thoratec Laboratories, Berkeley, Calif.) and the Abiomed device (Abiomed, Danvers, Mass.) are included in this category.

§The Novacor left ventricular assist system (Baxter Healthcare, Oakland, Calif.) and the Heartmate left ventricular assist device (ThermoCardiosystems, Woburn, Mass.) are included in this category.

¶The Cardiowest artificial heart (Cardiowest, Tucson, Ariz.) and the Penn State pneumatic artificial heart are included in this category.

largely because of concern that pneumatically activated devices could not be sufficiently miniaturized to provide a suitable quality of life. At the time, the available devices required patients to be tethered to bulky external power sources that restricted mobility and independence.

The 1980s marked the first implantation of a pneumatic total artificial heart (Jarvik-7-100) by DeVries et al.²⁶ Shortly thereafter, Copeland et al. described a long-term survivor who had received a total artificial heart as a bridge to cardiac transplantation.²⁷ The initial enthusiasm for implantation of the total artificial heart soon faltered; the high incidence of thromboembolic events²⁸ and severe infections^{29,30} and the low survival rates culminated in 1991 with a moratorium on the use of the Jarvik heart in the United States.²⁸

By then, a multicenter clinical evaluation of left ventricular assist devices as a bridge to transplantation had demonstrated a 65 percent rate of survival to transplantation, as compared with 50 percent for medically treated patients.²¹ On the basis of this and other studies,^{31,32} the Food and Drug Administration (FDA) approved the use of a left ventricular assist device with an external power source as a bridge to transplantation in 1994.

In this decade, technological advances in the design of left ventricular assist devices, biomaterials, and miniaturization have eliminated bulky external

TABLE 2. LANDMARK EVENTS IN THE DEVELOPMENT OF VENTRICULAR ASSIST DEVICES.

YEAR	EVENT
1954	Development of the cardiopulmonary-bypass machine
1964	Chartering of the Artificial Heart Program by the National Heart, Lung, and Blood Institute
1966	First use of a pneumatic device as a bridge to recovery
1967	First human heart transplantation
1969	First successful use of a pneumatic total artificial heart as a bridge to transplantation
1970s	Development of a variety of extracorporeal and implantable pneumatic ventricular assist devices
1974	Redirection of the efforts of the Artificial Heart Program toward the development of implantable devices
1984	First implantation of a total artificial heart as a permanent device
1985	Multicenter evaluation of left ventricular assist devices as a bridge to transplantation
1991	Moratorium on the use of the total artificial heart
1993	FDA approval of a New Investigational Device exemption for a total artificial heart
1994	FDA approval of a left ventricular assist device as a bridge to transplantation
1994	First use of a wearable left ventricular assist device
1996–present	Recruitment of patients for a randomized trial comparing wearable left ventricular assist device with medical therapy

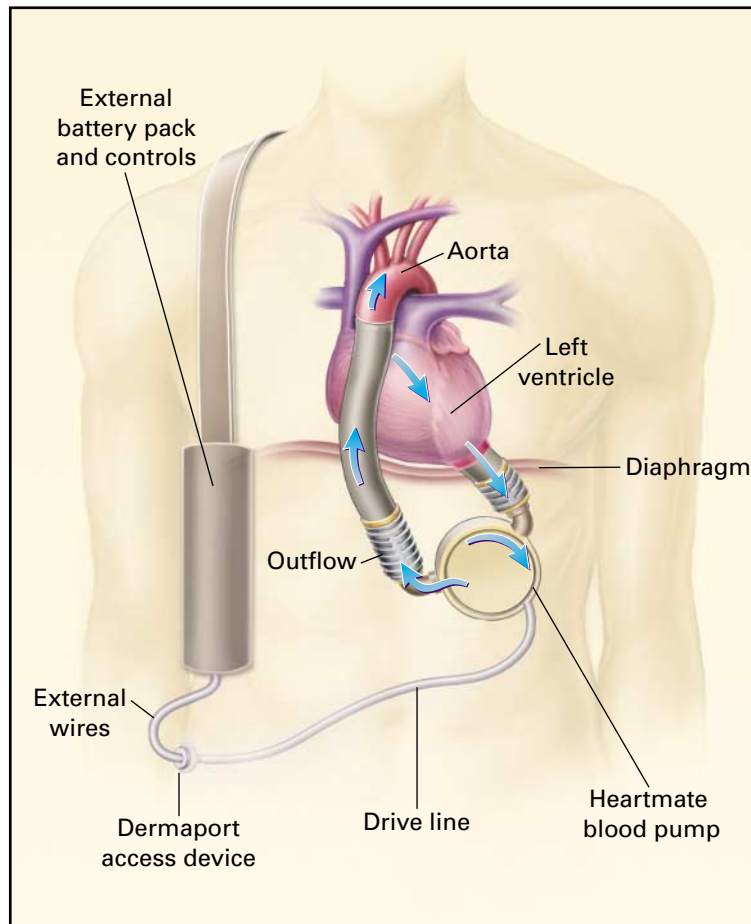


Figure 1. A Wearable Left Ventricular Assist Device and Its Components.

The inflow cannula is inserted into the apex of the left ventricle, and the outflow cannula is anastomosed to the ascending aorta. Blood returns from the lungs to the left side of the heart and exits through the left ventricular apex and across an inflow valve into the pumping chamber. Blood is then actively pumped through an outflow valve into the ascending aorta. The pumping chamber is placed within the abdominal wall. One transcutaneous line carries the electrical cable and air vent to the battery pack and electronic controls, which are worn on a shoulder holster or belt.

consoles, and wearable systems have performed remarkably well in patients awaiting transplantation. With existing devices, 91 percent of patients with severe congestive heart failure can be discharged from the hospital, and 74 percent survive to undergo transplantation.³³ The goal of fully implantable systems has yet to be attained, however, largely because of problems of reliability.

WEARABLE LEFT VENTRICULAR ASSIST DEVICES

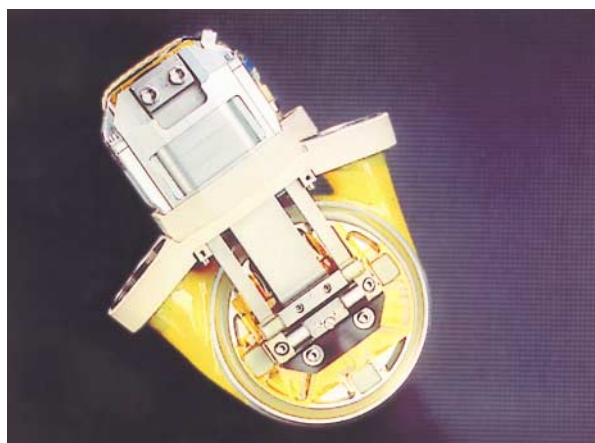
Technological advances in miniaturization have resulted in the development of electrically powered, wearable left ventricular assist devices that allow patients to leave the hospital and resume an independent existence (Fig. 1). The current state of the art is represented by two systems, the ThermoCardiosys-

tems Heartmate 1205 VE device (ThermoCardiosystems, Woburn, Mass.) and the Novacor N100 left ventricular assist system (Baxter Healthcare, Oakland, Calif.). Both devices are implanted through a median sternotomy with an inflow cannula inserted into the left ventricular apex and an outflow tube anastomosed to the ascending aorta. The pumping chamber is placed within the abdominal wall.³⁴

Both devices can be operated either in a fixed-rate mode or, more often, in an automatic mode that more closely resembles normal physiologic conditions.³⁵ In the automatic mode, the device ejects when the pump is 90 percent full or when it senses a decreased rate of filling. As the patient's activity increases, the pump fills faster and the rate (or stroke volume) automatically increases, resulting in an increase in pump output. With a decrease in activity,



A



B

Figure 2. Two Left Ventricular Assist Devices.

Panel A shows the pumping chamber of the opened ThermoCardiosystems device. The textured polyurethane diaphragm covered by a thin neointimal lining is shown on the left, and the sintered titanium housing is shown on the right. Panel B shows the unencapsulated pump-drive unit of the Novacor left ventricular assist system.

pump filling and output decrease. Because the aortic valve rarely opens when the heart is being supported by a left ventricular assist device, pump output is synonymous with cardiac output.

Both devices can deliver a cardiac output of up to 10 liters per minute and have similar stroke volumes and maximal rates. The Heartmate system uses textured biologic surfaces (Fig. 2A). Blood is expelled from the device by a single pusher plate activated by a rotary electric motor. The Novacor device (Fig. 2B) uses smooth polyurethane biologic surfaces and requires that the patient receive long-term warfarin therapy. Electromagnetically activated double pusher plates power the system.

A single drive line containing the electrical cable and the atmospheric air vent leads transcutaneously from the implanted pump to the outside (Fig. 1). The line is covered with polyester velour that pro-

motes tissue bonding at the skin, firmly anchoring the line to the skin and reducing the risk of infection. Both devices are powered by two rechargeable batteries that provide four to six hours of charge and are usually worn in a shoulder holster, vest, or belt.

The wearable electrical devices currently available have external backup mechanisms to continue support without the need for reoperation in case of failure of the device.²⁴ If the device should fail, the native heart would usually be able to provide systemic support until the device could be examined. Because the electronic control unit is outside the body, it can easily be repaired should failure of the software, chip, or electronics occur. Finally, if the motor device fails, the single-pusher-plate device can be pneumatically activated with a hand-held portable pump.

Although much attention has focused on the development of esthetically appealing, fully implantable

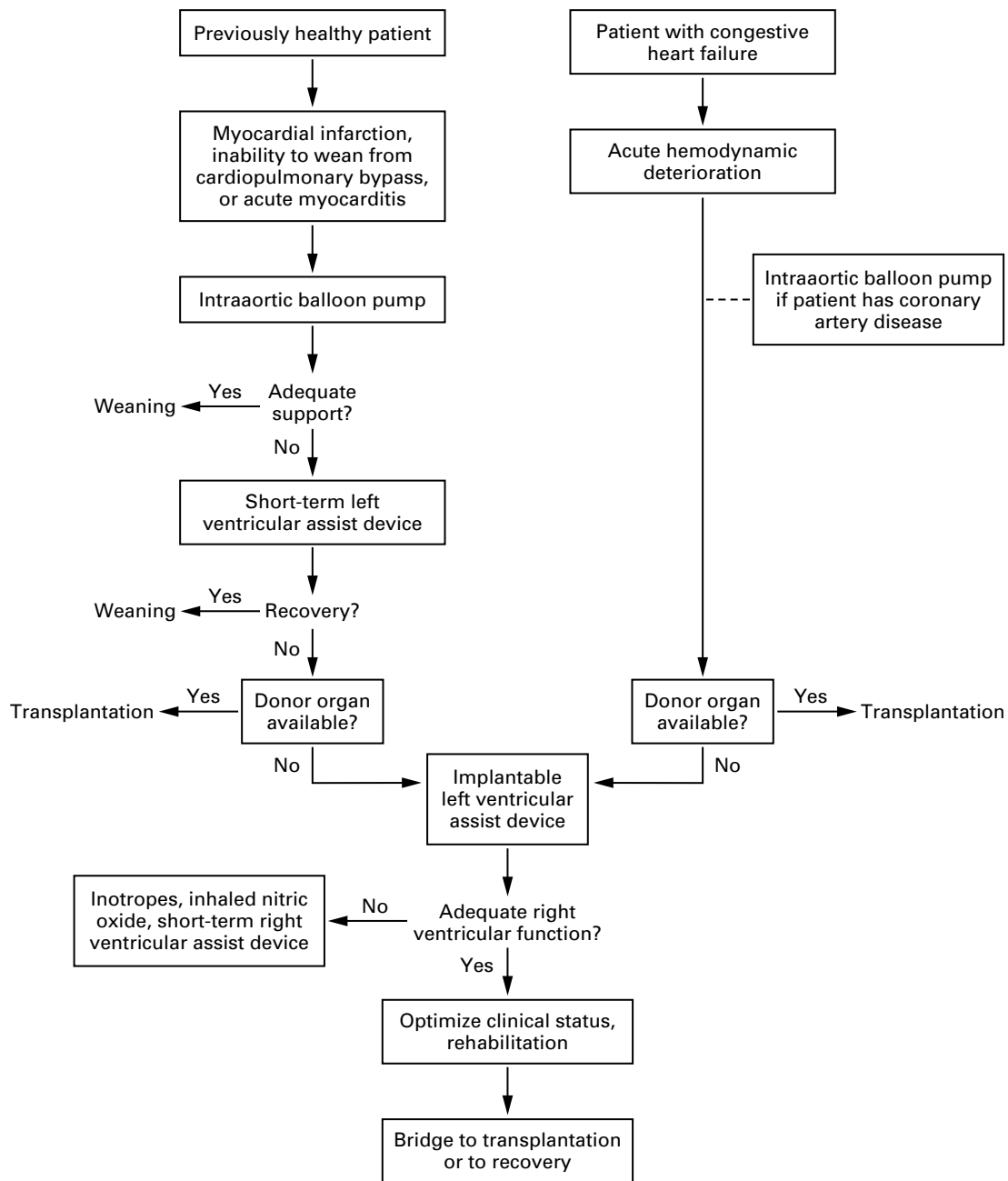


Figure 3. Scheme for Selection of Patients with Acute Cardiac Disease or Congestive Heart Failure for Implantation of Left Ventricular Assist Devices.

mechanical devices, a number of obstacles currently preclude their clinical use. With all pulsatile systems, a compliance chamber is necessary to compensate for air displacement.³⁶ Efforts to develop an implantable compliance chamber to avoid the need for external venting have met with recurrent technical problems relating to buildup of fibrous tissue and accumulation of water in the chamber and escape of gas from it.

LEFT VENTRICULAR ASSIST DEVICES AS A BRIDGE TO TRANSPLANTATION

Selection of Patients

Selection is a crucial consideration that determines the ultimate outcome of patients who receive a left ventricular assist device. In general, patients who have been selected to receive left ventricular as-

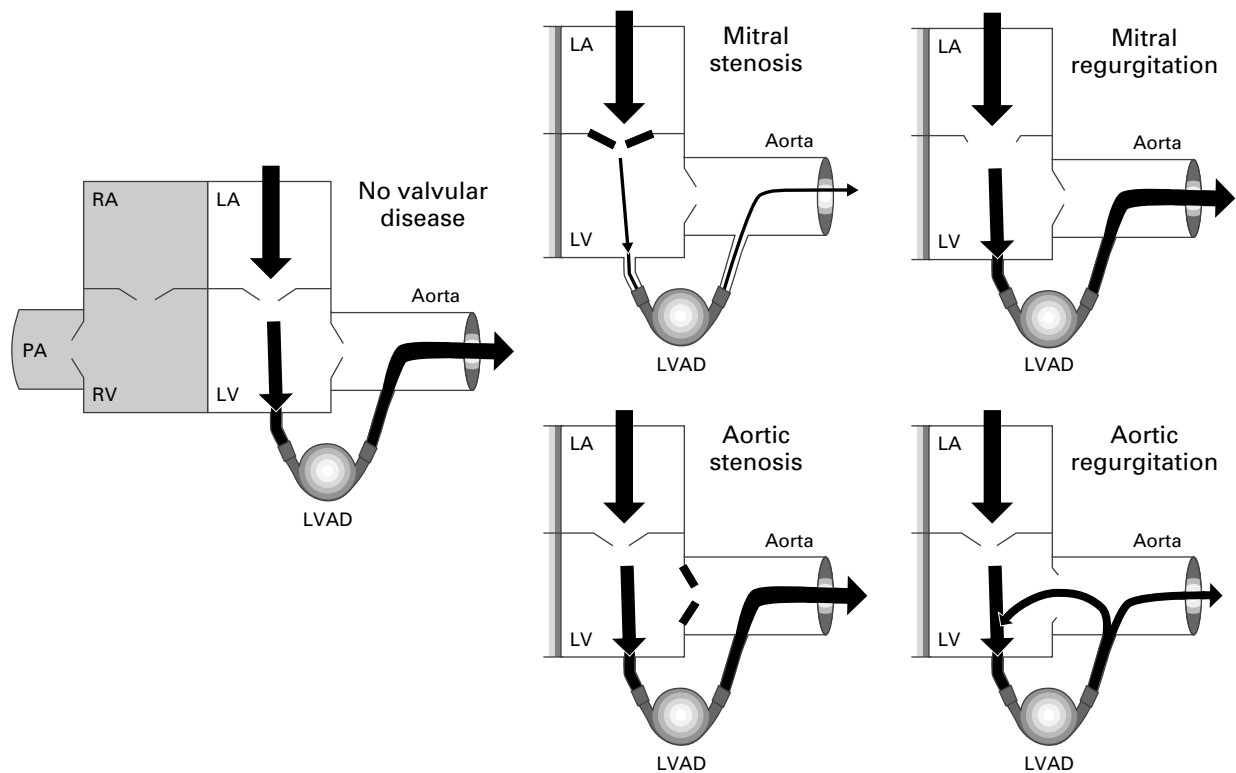


Figure 4. Physiology of Blood Flow through a Left Ventricular Assist Device (LVAD) in Patients with Valvular Heart Disease.

Mitral stenosis, if severe, will limit filling of the device and should be corrected. Mitral regurgitation does not limit the proper functioning of the device; complete unloading of the left ventricle after placement of the device results in complete afterload reduction of the left ventricle, eliminating mitral regurgitation. Mild aortic stenosis in the absence of insufficiency is not a contraindication to placement of a left ventricular assist device. If aortic insufficiency is present, blood pumped into the aortic root by the device will flow backward across the incompetent aortic valve (aortic regurgitation), thereby decreasing net forward flow and compromising end-organ perfusion. Even mild-to-moderate aortic insufficiency can become severe with institution of support from a left ventricular assist device, because the usually elevated left ventricular end-diastolic pressure will be reduced to nearly zero, whereas the base-line low systemic pressure will be elevated. Wide black bars indicate stenosis. PA denotes pulmonary artery, RA right atrium, RV right ventricle, LA left atrium, and LV left ventricle.

sist devices have end-stage heart disease without irreversible end-organ failure. For patients who are too ill to undergo heart transplantation, such as those who cannot be weaned from cardiopulmonary bypass, use of a short-term extracorporeal left ventricular assist device is a first-line therapy (Table 1). For patients who are suitable candidates to receive a heart transplant but are unlikely to survive the three-to-four-month wait currently required before transplantation, left ventricular assist devices are an effective bridge to transplantation. The Food and Drug Administration has recently approved the marketing of both the Heartmate system and the Novacor device for use as bridges to transplantation. Bridging is particularly valuable for large patients with type O blood and for patients with a positive panel-reactive-antibody titer for whom prospective cross-matching is required.³⁷ Although left ventricular assist devices have not yet been used in patients who

are not considered candidates for heart transplantation, such as those with severe diabetes mellitus or advanced age, left ventricular assist devices may ultimately be the preferred therapy. A commonly used scheme for the selection of patients for implantation of left ventricular assist devices is shown in Figure 3.

Cardiac Factors Affecting Selection

Valvular Heart Disease

Patients with preexisting mitral stenosis or aortic regurgitation may require correction of the valvulopathy before implantation of the device (Fig. 4).

Coronary Artery Disease

Patients with inoperable coronary artery disease sometimes continue to have angina without adverse hemodynamic effects while being supported by a left ventricular assist device. However, right ventricular ischemia and myocardial injury soon after implanta-

tion of the device can cause right-sided heart failure, resulting in decreased flow to the left ventricular assist device. In patients who have had coronary bypass surgery, efforts are made to preserve patent grafts in order to reduce the risk of perioperative right-sided ischemia and arrhythmias. On occasion, surgery is performed to bypass lesions of the right coronary artery at the time of implantation of the device, in an attempt to optimize perioperative right-sided heart function.

Arrhythmias

Atrial and ventricular arrhythmias, which are common in patients with cardiomyopathies, continue to occur after implantation of the device.³⁸ Atrial fibrillation hinders right ventricular filling but is reasonably well tolerated in recipients of left ventricular assist devices.

Severe ventricular arrhythmias were previously believed to be a contraindication to univentricular support. Recent experience, however, has revealed no serious hemodynamic compromise in patients in whom these arrhythmias develop in the late postoperative period. In a 1994 study,³⁹ 9 of 21 recipients of left ventricular assist devices had severe ventricular arrhythmias 0 to 186 days after implantation of the device. The mean arterial and central venous pressures were not changed by the arrhythmias. The flow through the device decreased by an average of 1.4 liters per minute at the onset of the arrhythmia but returned to normal after cardioversion. No syncope, thromboembolic events, or major end-organ dysfunction occurred. During ventricular fibrillation and in the absence of pulmonary hypertension, recipients of left ventricular assist devices tolerate the equivalent of a Fontan (systemic vein to pulmonary artery) circulation. Nonetheless, early electrical or pharmacologic cardioversion is warranted to avoid thrombus formation and improve exercise tolerance.

Congenital Defects

Intracardiac septal defects should be repaired at the time of implantation of the device to avoid the right-to-left shunt and subsequent oxygen desaturation that would be created by the sudden reduction in left filling pressures.⁴⁰

Extracardiac Factors Affecting Selection

Patients undergoing implantation of a device as a bridge to heart transplantation often have end-organ dysfunction related to long-term cardiac insufficiency. They are usually chronically debilitated and must withstand the rigors of two operations (device implantation and heart transplantation), with the risks entailed by immunosuppressive therapy after the second operation. Functional compromise of end-organs must be carefully considered in selecting candidates for implantation of left ventricular assist devices.

The presence of irreversible major neurologic deficits is a contraindication to implantation of a left ventricular assist device and heart transplantation. Severe obstructive or restrictive pulmonary disease is also a contraindication, because these patients often have oxygen desaturation in the perioperative period that can result in hypoxic pulmonary vasoconstriction and right-sided heart failure. Decreased pulmonary diffusion capacity, on the other hand, is common in patients with heart failure⁴¹ (especially those receiving amiodarone⁴²) and is not considered a contraindication. Moderately elevated pulmonary vascular resistance is also commonly encountered⁴³ and does not preclude successful implantation of a device, particularly if the central venous pressure is low.

Although dependence on hemodialysis is a contraindication to implantation of a device, moderate renal insufficiency due to low cardiac output does not preclude it. In patients with such renal insufficiency, renal function improves as hemodynamics improve and the need for vasoconstricting drugs is reduced. Continuous venovenous hemofiltration is often necessary in the postoperative period to facilitate fluid management in these patients.

Preoperative hepatic insufficiency manifested by elevated prothrombin times is present in most patients with right-sided heart failure. Perioperative bleeding, to which these patients are prone, will further exacerbate right-sided heart failure and lead to increasing hepatic congestion and coagulopathy. Any coagulopathy present before surgery should be corrected aggressively. Persistence of a prothrombin time greater than 16 seconds usually contraindicates placement of a device.⁴⁴ Arterial and aortoiliac disease of the lower extremities complicates transfemoral institution of cardiopulmonary bypass, which is sometimes necessary at the time of removal of the device.

Additional factors that may complicate placement of a device and compromise survival include long-term glucocorticoid therapy and small body-surface area (less than 1.5 m²). The complication due to small body-surface area results from the need to implant the pumping chamber of the device beneath the abdominal wall without causing excessive disruptive force on the wound.

Finally, the development of long-term implantable devices that allow patients to be discharged to their homes has imposed the need to assess a patient's ability to manage the device before implantation can be offered. The presence of a constant companion, though desirable, is no longer required.

Interactions between the Patient and the Device

Left ventricular assist devices used as a bridge to transplantation restore near-normal resting hemodynamics and reasonable exercise tolerance. In a recent assessment of submaximal exercise capacity, patients

with left ventricular assist devices performed significantly better on a six-minute walk testing than dobutamine-dependent patients and similarly to patients with mild heart failure. The mean (\pm SE) distance covered was 476.1 ± 123.1 m (1562 ± 404 ft) for 14 patients with left ventricular assist devices, 289.0 ± 73.5 m (948 ± 241 ft) for 20 patients receiving dobutamine, and 413.9 ± 84.7 m (1358 ± 278 ft) for 14 patients with heart failure ($P < 0.01$).⁴⁵ Similarly, oxygen consumption was also greater in the patients with left ventricular assist devices than in the other two groups (16.3 ± 6.5 ml per kilogram per minute for patients with left ventricular assist devices, 9.8 ± 4.8 ml per kilogram per minute for patients receiving dobutamine, and 11.2 ± 2.0 ml per kilogram per minute for patients with heart failure; $P < 0.05$). In patients studied five months after the institution of support with a left ventricular assist device, peak oxygen consumption was significantly better than that of patients with New York Heart Association class III heart failure.⁴⁶ In some patients, the peak oxygen consumption was higher than would be predicted from maximal pump flow, suggesting the recovery of native heart function.

The mechanical unloading afforded by the left ventricular assist device results in attenuation of the myocardial histologic abnormalities caused by chronic heart failure,⁴⁷ including normalization of fiber orientation,⁴⁸ regression of myocyte hypertrophy,⁴⁹ and reduction in myocyte wavy fibers and contraction-band necrosis.⁵⁰ Prolonged left ventricular unloading reverses ventricular dilatation, as demonstrated by an improvement in the end-diastolic pressure–volume relation.⁵¹ Long-term support with a left ventricular assist device improves the efficiency of myocardial mitochondria⁵² and results in a reduction in the neuroendocrine perturbations that accompany congestive heart failure (including abnormalities in plasma renin activity and plasma concentrations of angiotensin II, epinephrine, norepinephrine, and arginine vasopressin).^{53,54} Many centers have reported patients with left ventricular assist devices whose myocardial function improved enough to allow removal of the device, rather than the previously necessary heart transplantation, a scenario now termed a “bridge to myocardial recovery.”^{51,55}

Another valuable lesson learned from the experience with left ventricular assist devices as a bridge to transplantation is that the use of porcine inflow and outflow valves and a wandering-vortex blood-flow pattern can reduce the risk of thromboembolism.⁵⁶ Increasing evidence points to interactions between the host (patient) and the graft (the surface of the left ventricular assist device) that maintain a delicate balance between activated procoagulant and fibrinolytic cascades. A recent study documented the presence of sustained thrombin generation and fibrinolysis in patients with left ventricular assist devices,

despite their normal values on routine coagulation tests.⁵⁷ The low incidence of thromboembolic events in recipients of textured-surface left ventricular assist devices suggests that this low-grade disseminated intravascular coagulopathy reduces the risk of clinically important thromboembolism. Absorption of tissue macrophages that express tissue factor by the surface of the device may be the trigger that generates this systemic procoagulant state.⁵⁸

Patients' Adaptation to the Device

Surgical intervention should not only restore normal resting hemodynamics but also provide the patient with substantial improvement in the quality of life. Debilitated recipients of left ventricular assist devices require weeks of aggressive nutritional support and rehabilitation to restore muscle mass and strength. Early in the postoperative period, patients begin a rehabilitation program that encourages progressive mobilization from walking to treadmill exercise to cycling. These programs have promoted optimal physical recovery before heart transplantation,⁵⁹ and in most instances they facilitate the patient's discharge home. Furthermore, the autonomy gained unquestionably increases the patient's emotional well-being.^{60,61}

After implantation of a left ventricular assist device, patients can often return to work and engage in other activities, including gardening, dancing, and driving.²³ Of 24 patients treated by us who were discharged home on mechanical support, 6 returned to school and 5 returned to work. Only activities that would result in the submersion of percutaneous lines (such as swimming) are proscribed, although showering is possible with special precautions for the air vent.

COMPLICATIONS

Bleeding, right-sided heart failure, air embolism, and progressive multisystem organ failure are the most common causes of early morbidity and mortality after placement of a left ventricular assist device. The most common complications in the late postoperative period are infection, thromboembolism, and failure of the device.

Bleeding

Hemorrhage is the most common complication associated with placement of a left ventricular assist device. In the early experience, about 50 percent of patients required reoperation for bleeding,⁶² but the risk of major hemorrhage has decreased to about 30 percent with the use of the serine protease inhibitor aprotinin.⁶³ Perioperative hemorrhage can have many causes, including preoperative coagulopathy due to hepatic dysfunction, poor nutritional status, and antibiotic therapy; cardiopulmonary-bypass–induced thrombocytopenia and platelet dysfunction; and the

extensive nature of the surgery, which requires median sternotomy, cardiac mobilization (often in patients who have had previous cardiac surgery), and extensive dissection of the abdominal wall to create a pocket for the pump.

Right-Sided Heart Failure

Hemodynamic stability can be attained with isolated mechanical left ventricular support in more than 90 percent of patients,⁶⁴ even in those with substantial right ventricular dysfunction, if there is effective replacement of left-sided heart function and treatment of pulmonary hypertension.

Historically, right-sided heart failure of sufficient severity to warrant the use of a right ventricular assist device occurred in nearly 20 percent of recipients of left ventricular assist devices²¹ and was the leading cause of perioperative death for patients undergoing placement of a left ventricular assist device.⁶² More recently, improved perioperative management, including the use of inhaled nitric oxide,^{65,66} has reduced the need for placement of a right ventricular assist device. The need was reduced from 15 percent (8 of 55 patients) to 7 percent (3 of 45 patients) after the introduction of nitric oxide at our institution.⁶⁷

Right-sided heart failure is usually associated with perioperative hemorrhage and the need for blood transfusion.⁶³ Right-sided heart failure rarely develops in patients who do not have major bleeding in the perioperative period. It may be cytokine-mediated; hemorrhage and resuscitation increase the production of several cytokines, including interleukin-1 β , interleukin-6, and interleukin-10, as well as tumor necrosis factor α .⁶⁸ Tumor necrosis factor α can induce pulmonary hypertension,⁶⁹ and its effect may be mediated by platelet-activating factor,^{70,71} a potent vasoconstrictor of the pulmonary circulation.^{72,73}

Thromboembolism

Historically, thromboembolic events occurred in about 20 percent of patients receiving a left or right ventricular assist device.³³ In a more recent multicenter study,⁷⁴ the total thromboembolic event rate was 0.01 per patient-month of device use among 223 patients supported with a Heartmate left ventricular assist device over a total support time of 531 patient-months. This low incidence has been attributed to the use of textured blood-contacting surfaces.^{57,58,74} Because of the low incidence of thromboembolic events, most patients receiving this device do not require long-term anticoagulant therapy with warfarin but instead receive only an antiplatelet drug such as aspirin. Intraoperative air embolism occurs rarely because the devices are cleared of air and the left ventricle is filled before the device is activated. Prospective transcranial Doppler examinations have documented asymptomatic cerebral microemboli in

34 to 67 percent of recipients of left ventricular assist devices.^{75,76}

Infection

Recipients of left ventricular assist devices are prone to nosocomial and device-related infections. The former occur as a result of the patient's prolonged hospitalization, immobilization, endotracheal intubation, suboptimal nutritional status, and need for multiple intravascular and bladder catheters.^{77,78} The most common infections in recipients of the device — those related to the drive line — remain confined to the exit site and are manageable with local wound care and antibiotics. Infections in the abdominal-wall pocket holding the device require more aggressive treatment, including open drainage, débridement, and rerouting of the drive line through a fresh exit site. On very rare occasions, supervening sepsis necessitates replacement of the device.⁷⁷ Fortunately, these infections do not preclude heart transplantation.^{79,80} According to a review of more than 2000 patients in 73 centers worldwide,³⁴ clinically important infections occurred in 25 percent of recipients of left ventricular assist devices.

Device Malfunction

Anecdotal reports of device malfunction have appeared.⁸¹ Among 14 outpatients with left ventricular assist devices in one series, there were 29 controller malfunctions during 1640 days of support.²³ None of the malfunctions threatened the ability of the device to provide adequate blood flow, and all were easily repairable.

Other Complications

Hemolysis has been described in patients with centrifugal- and axial-flow left ventricular assist devices,⁸² but it has not been a clinical problem in patients with implantable left ventricular assist devices. On occasion, placement of a left ventricular assist device has been associated with transient early satiety and inability to tolerate oral intake.⁸³

FUTURE DIRECTIONS

Long viewed as an unattainable goal, long-term mechanical support as a useful therapy for patients with end-stage heart disease seems inevitable; these patients will probably be in a situation similar to that of patients with end-stage renal disease. Patients with heart failure that progresses to end-stage heart disease may eventually undergo placement of a left ventricular assist device, with the option of indefinite mechanical support or heart transplantation in the event that a donor organ becomes available.

The bridge to recovery is a theoretically attractive application for this technology. There is increasing understanding of the mechanisms that lead to cardiac remodeling and recovery of left ventricular func-

tion^{51,55} and of the factors that predict the ability of a patient to function successfully after the removal of a left ventricular assist device, without receiving a heart transplant. Several methods have been proposed to predict successful weaning from and removal of a left ventricular assist device,^{55,84-86} including exercise testing while flow through the device is reduced substantially. Although successful explantation of a device without heart transplantation remains desirable, the experience in such cases is anecdotal,^{57,87} and the long-term function and survival of the patients are unknown.

The increased use of mechanical support in patients with end-stage heart disease may improve the outcome of heart transplantation, because the hemodynamic and clinical benefits of mechanical assistance can convert high-risk, terminally ill patients into stable, reconditioned heart-transplant recipients. Because these patients can return to their homes while awaiting transplantation, the need for and costs of hospitalization should be reduced. More important, survival after transplantation may be higher as healthier patients undergo transplantation. We know of at least 40 patients who have received mechanical support for more than 300 days, and a growing number are returning to normal activities.

Modification of the devices to increase long-term reliability and reduce infectious and thromboembolic complications may be necessary before they can be used widely. At present, three classes of device are at advanced stages of preclinical development. One is a new generation of pneumatic, direct mechanical ventricular assist devices that are wrapped around the heart and do not directly contact the blood. The second consists of compact axial-flow pumps that do not require a compliance chamber and are capable of delivering a high cardiac output. The third is represented by the reapproved pneumatic total artificial heart.⁸⁸ The artificial heart may have a role as a bridge to transplantation for a subgroup of patients with severe biventricular dysfunction and a fixed increase in pulmonary vascular resistance in whom left ventricular support may not be sufficient. Obligatory systemic anticoagulant therapy, restricted mobility, and lack of experience with the long-term use of the devices, however, limit their applicability as a means of permanent mechanical support.

The future of mechanical support will probably be shaped by the results of an ongoing study comparing the use of a left ventricular device with medical therapy²⁴ and by the forthcoming availability of smaller, fully implantable devices.

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