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Improved Mortality and Rehabilitation of Transplant Candidates Treated with a Long-Term Implantable Left Ventricular Assist System

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Objective

This nonrandomized study using concurrent controls was performed to determine whether the HeartMate implantable pneumatic (IP) left ventricular assist system (LVAS) could provide sufficient hemodynamic support to allow rehabilitation of severely debilitated transplant candidates and to evaluate whether such support reduced mortality before and after transplantation.

Methods

Outcomes of 75 LVAS patients were compared with outcomes of 33 control patients (not treated with an LVAS) at 17 centers in the United States. All patients were transplant candidates who met the following hemodynamic criteria: pulmonary capillary wedge pressure $\geq$ 20 mm Hg with a systolic blood pressure $\leq$ 80 mm Hg or a cardiac index $\leq$ 2.0 L/minute/m^2. In addition, none of the patients met predetermined exclusion criteria.

Results

More LVAS patients than control patients survived to transplantation: 53 (71%) *versus* 12 (36%) ($p = 0.001$); and more LVAS patients were alive at 1 year: 48 (91%) *versus* 8 (67%) ($p = 0.0001$). The time to transplantation was longer in the group supported with the LVAS (average, 76 days; range, <1–344 days) than in the control group (average, 12 days; range, 1–72 days). In the LVAS group, the average pump index (2.77 L/minute/m^2) throughout support was 50% greater than the corresponding cardiac index (1.86 L/minute/m^2) at implantation ($p = 0.0001$). In addition, 58% of LVAS patients with renal dysfunction survived, compared with 16% of the control patients ($p < 0.001$).

Conclusions

The LVAS provided adequate hemodynamic support and was effective in rehabilitating patients based on improved renal, hepatic, and physical capacity assessments over time. In the LVAS

group, pretransplant mortality decreased by 55%, and the probability of surviving 1 year after transplant was significantly greater than in the control group (90% *vs.* 67%, p = 0.03). Thus, the HeartMate IP LVAS proved safe and effective as a bridge to transplant and decreased the risk of death for patients waiting for transplantation.

The death rate for patients awaiting cardiac transplantation continues to rise because of the scarcity of donor organs and a progressive increase in the waiting period for a donor heart. Whereas the number of heart transplants performed in the United States remains relatively unchanged at approximately 2000 per year, the number of patients on the waiting list for this procedure has increased progressively.[1,2] Of the 29,212 patients registered by the United Network for Organ Sharing from January 1, 1988, to August 1994, 3937 (13.5%) died while awaiting transplant.[3] Moreover, between 1988 and 1993, the number of transplant candidates who died while on the waiting list increased by 55%, from 492 to 762.[4] As the list continues to grow because of expansion of the number of transplant centers and broadening of acceptance criteria, the death rate for patients awaiting transplantation is expected to increase even further.

Because transplant candidates in severe nonreversible left ventricular failure are at heightened risk of dying before a donor organ becomes available, left ventricular assist devices have been used to provide hemodynamic support to these patients, which has been effective in improving their survival.[5–8] Left ventricular assist devices have yielded encouraging results in postcardiotomy,[9,10] postinfarction,[11] and end-stage cardiomyopathy patients.[12,13] Although the median waiting time (defined as the number of days that elapsed before half of the patients registered during a given year underwent transplants for which they were registered) for heart transplantation increased from 108 days in 1988 to 208 days in 1993,[4] left ventricular assist systems (LVASs) have been shown to provide adequate hemodynamic support for comparable periods, with implant durations ranging up to 503 days.[14]

The HeartMate implantable pneumatic (IP) LVAS (Thermo Cardiosystems, Inc., Woburn, MA) was originally developed in response to the National Heart, Lung, and Blood Institute's 1980 Request for Proposal (RFP NHLBI 80-3). This request for proposal called for the development of a long-term, implantable electrically powered LVAS. With the introduction of cyclosporine and the concomitant renewed interest in transplantation in the early 1980s, the need arose for a device that could be used to keep severely ill patients alive until transplant. Norman and associates[15] had first used a left ventricular assist device in 1978 as a bridge to transplant. This device kept the patient alive for 5 days until a donor heart could be found; the patient died later of infectious complications related to the panimmune suppressive effect of Imuran. Although the HeartMate was originally designed for electrical power, the device was easily adapted to a less expensive pneumatic power source. In 1985, the pneumatic version received an Investigational Device Exemption from the Food and Drug Administration for use as a bridge to transplant.[16] This report summarizes the results of a nonrandomized study using concurrent clinical controls to assess the safety and effectiveness of the HeartMate IP LVAS in rehabilitating transplant candidates and reducing mortality.

MATERIALS AND METHODS

Device

The HeartMate IP LVAS is a pulsatile ventricular assist system that consists of an implantable pusher-plate blood pump, an interconnecting driveline, and an external drive console. The blood pump provides left ventricular support, and the console generates and controls pneumatic power to drive the blood pump through the interconnecting driveline.

The blood pump is positioned in the upper left abdominal quadrant, either beneath the diaphragm or preperitoneally. Its rigid titanium housing is divided into air and blood chambers by a flexible diaphragm. Blood drains from the left ventricle into the pump chamber; the diaphragm is then displaced by pressurized air, ejecting blood into the ascending aorta. The pump can produce an effective stroke volume of 83 mL, and blood flows up to 11.5 L/minute.

The pump's internal surfaces are covered with textured biomaterials that interface with the blood. Sintered titanium microspheres are used on the pump housing and conduits, and integrally textured polyurethane is used on the flexing pusher-plate diaphragm. The textured surfaces of the HeartMate promote the formation of a thin, well-adherent, pseudoneointimal lining on the inside of the pump. Since the early 1960s, blood cells have been shown to adhere to similar textured surfaces. In 1963, Jordan and associates[17] demonstrated that a

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hub of Dacron suspended in the bloodstream of a pig became coated with endothelial cells. The origin of these cells remains controversial.

Because this pseudoneointimal lining serves as the primary blood-contacting interface, minimal anticoagulation is needed. Cardiopulmonary bypass and systemic heparinization are required for LVAS implantation. Once the LVAS has been successfully implanted, protamine sulfate is administered to reverse the effects of the heparin. Thereafter, 10% low-molecular-weight dextran is given until the patient can accept oral medications. Throughout the remainder of the support period, inhibition of platelet activity is accomplished with dipyridamole and aspirin. The ability to limit postoperative anticoagulation to an antiplatelet regimen is attributed to the presence of not only textured surfaces but also porcine bioprosthetic valves. Although Coumadin may be required for medical management of these patients, it is not required for use of this pump.

The microprocessor-controlled console generates programmed pulses of air to drive the implanted blood pump. The console operates on either battery power or alternating current. The combination of an implanted blood pump with a portable external console allows the patient free mobility (Fig. 1).

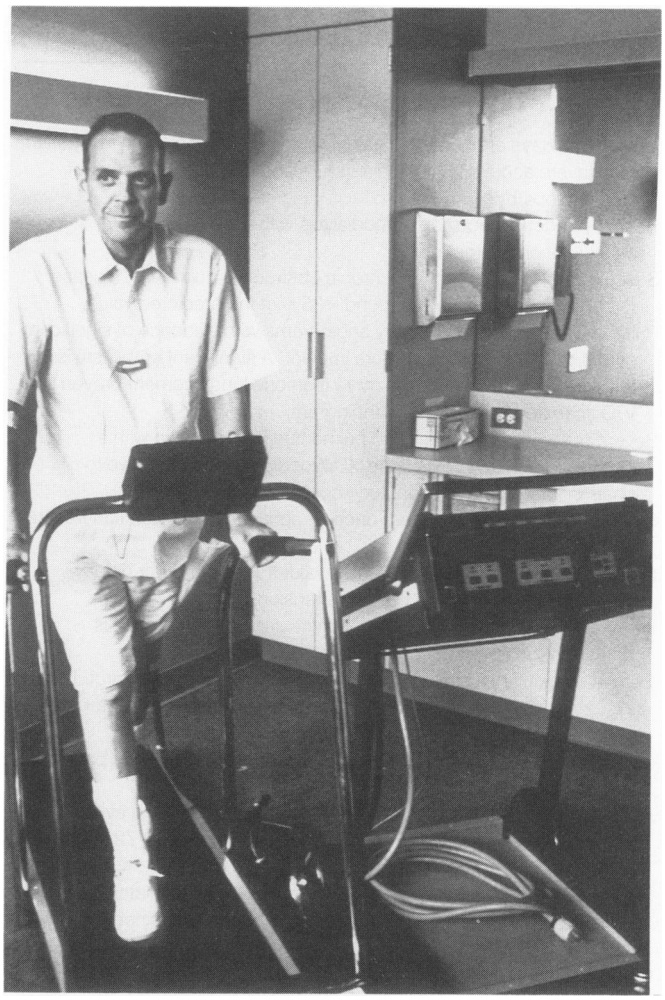

Figure 1. Patient shown during treatment with HeartMate IP LVAS. The portable external console allows the patient free mobility.

Population

Between August 1985 and September 1993, 108 nonrandomized patients were enrolled at 17 clinical centers within the United States (see the Appendix). Informed consent and patient data were obtained in compliance with protocols approved by each institution's investigational review board. All 108 patients had been approved for heart transplantation.

Seventy-five patients received a HeartMate IP LVAS. This group consisted of 64 males (85%) and 11 females (15%), whose average age was 45 years (range, 14–66 years). These patients met none of the predetermined exclusion criteria (Table 1) and all of the following hemodynamic indications for LVAS use: pulmonary capillary wedge pressure of ≥20 mm Hg, with either a cardiac index of ≤2.0 L/minute/m^2 or a systolic blood pressure of ≤80 mm Hg. All 75 patients were enrolled within 24 hours of meeting the selection criteria.

A concurrent group of 33 patients who met all the criteria for implantation of this device but who did not undergo LVAS treatment (either a device was unavailable or they refused treatment) were designated the control group. This group consisted of 26 men (79%) and 7 women (21%), with an average age of 48 years (range, 21–67 years). These patients were categorized as either prospective (n = 18) or retrospective (n = 15), depending on how they were selected and the methods used for data collection.

The 18 prospective control patients were identified in real time, and the data were obtained concurrently, as in the LVAS group. These control patients qualified for LVAS implantation but failed to receive the device, either because it was not available or because they refused such treatment.

The 15 retrospective control patients were selected as follows: each institution reviewed its transplant data base and, without knowing the outcome, identified persons who had been approved for transplantation, were receiving intra-aortic balloon pump support and/or inotropic agents, and met the patient selection criteria for LVAS implantation. Data were collected from each patient's medical records at intervals designated by the study protocol, as in the LVAS group. The retrospective control patients received concurrent hospital care during the same period as the LVAS group, but they did not receive

Table 1. EXCLUSION CRITERIA

Body surface area <1.5 m^2.
Age >70 yr.
Less than 7 days after onset of an acute myocardial infarction in a patient with severe acute left ventricular failure and no previous history of cardiomyopathy.
Renal dysfunction requiring hemodialysis within 1 mo before consideration for implant.
Severe emphysema or severe chronic obstructive pulmonary disease: forced expiratory volume/second <35% of the predicted value.
Pulmonary infarction: pulmonary angiograms with evidence of significant embolism within 2 weeks before implant. A significant embolism is one that causes lung infarction in more than one lung segment proven by a V/Q scan and/or pulmonary angiogram.
Severe pulmonary disease: fixed pulmonary hypertension with a pulmonary vascular resistance >8 Wood units unresponsive to pharmacologic intervention, oxygen, etc.
Severely depressed right heart function: right ventricular ejection fraction estimated at <10%.
Severe hepatic disease: total bilirubin values >10 mg/dL or biopsy proven liver cirrhosis or portal hypertension.
Intractable ventricular tachycardia: ventricular tachycardia that is unresponsive to all conventional medical treatment.
Cerebral vascular disease: previous stroke with unresolved carotid bruit. History of strokes or transient ischemic attacks due to cerebral vascular disease.
Severe gastrointestinal malabsorption: steatorrhea or need for pancreatic enzyme replacement.
Active systemic infection: positive blood culture with clinical evidence of sepsis unresponsive to culture specific antibiotics within 72 hr before implant.
Severe blood dyscrasia: PT >16.0 sec; PTT >45.0 sec; platelet count <50,000/ml; clinical history of bleeding. All values obtained off anticoagulation.
Cancer, unresolved malignancy.
Nonreconstructible vascular disease including presence of limb or chest pain.
Refractory anuria: urine output <20 mL/hr in the presence of adequate renal perfusion.
BUN >100 mg/dL.
Creatinine >5.0 mg/dL.
Prolonged (>60 min) unsuccessful attempts to resuscitate the fibrillating heart.
Positive HIV test.
Long-term high dose steroid treatment: continuous use of steroids for a period >6 mo with a dose ≥20 mg/day.

an LVAS because the device was not available when treatment was required.

The key demographic characteristics were similar in the LVAS and control groups regarding age, sex, and distribution of patients with ischemic cardiomyopathy, idiopathic cardiomyopathy, and subacute myocardial infarction (Table 2).

Data Collection

Hemodynamic, renal, and hepatic data were collected at baseline and then weekly until the patient either underwent transplantation or died. Baseline for the LVAS patients was defined as the 24-hour period before device implantation. For the control patients, a baseline was defined as the point in time when the patient met all the criteria for use of the LVAS, including the hemodynamic criteria. Hemodynamic data included cardiac index (cardiac output/body surface area) and pump index (pump flow/body surface area). Renal function was evaluated on the basis of creatinine and blood urea nitrogen (BUN) levels. Hepatic function was monitored by assessing total bilirubin, serum glutamic oxaloacetic transaminase, and serum glutamic pyruvic transaminase levels.

In the LVAS group, the New York Heart Association functional class was also assessed at baseline and after LVAS implantation. Each patient was assigned a value ranging from class IV (poor functional capacity) to class I (good functional capacity).

Adverse Events

The following key adverse events were monitored: bleeding, hemolysis, infection, right ventricular failure, embolic events, and renal dysfunction.

Bleeding. Bleeding was monitored only in the LVAS group, because the control patients did not undergo surgery. As defined in this study, bleeding involved a serious enough blood loss (e.g., cardiac tamponade) to necessitate returning the patient to the operating room or to cause death. Furthermore, bleeding was reported if it arose directly from the device itself, including the connectors or grafts, or from the abdominal implant site.

Hemolysis. Hemolysis was deemed to be present when two consecutive plasma-free hemoglobin studies yielded levels of >40 mg/dL.

Infection. Systemic infection was indicated by positive blood, urine, sputum, or tissue cultures, coupled with an elevated white blood cell count (≥12,500/mL), fever (≥38.1 C), and treatment with antimicrobial drugs.

Table 2. DEMOGRAPHIC CHARACTERISTICS

Variable	LVAS Group (n = 75)	Control Group (n = 33)
Average age (yr) (SD)	45 (13)	48 (12)
Median age (yr) (range)	49 (14–66)	48 (21–67)
Gender		
Men (%)	64 (85)	26 (79)
Women (%)	11 (15)	7 (21)
Diagnosis		
Ischemic cardiomyopathy	31 (41)	20 (61)
Idiopathic cardiomyopathy (%)	39 (52)	12 (36)
Subacute myocardial infarction (%)	5 (7)	1 (3)

Table 3. SURVIVAL RATES*

Variable	LVAS Group (n = 75)	Control Group (n = 33)
Underwent transplantation (%)	53 (71)	12 (36)
Alive 60 days after transplant (%)	49 (65)	10 (30)

* According to Fisher's exact test, both intergroup differences were significant (p = 0.001).

For LVAS patients, driveline infection was documented when positive cultures were obtained from the exit site and treatment with antimicrobial agents was necessary.

Right Ventricular Failure. Right ventricular failure was defined as an inability to provide sufficient flow from the right ventricle to the left ventricle, necessitating the use of a right ventricular assist device.

Embolic Events. An embolic event was characterized by clinical symptoms of stroke or by sudden neurologic, pulmonary, renal, hepatic, or peripheral vascular changes. Embolic events were further classified according to whether they were attributed to septic emboli or thromboemboli.

Renal Dysfunction. Renal dysfunction was indicated by a serum creatinine level of ≥2.2 mg/dL or a BUN value of ≥50 mg/dL.

Statistical Analyses

Univariate statistical analyses were performed to test the hypothesis that the transplantation and survival rates for the LVAS patients were greater than those for the control group. Univariate tests of association were performed, using Fisher's exact test for 2 × 2 comparison. Intergroup actuarial survival after transplantation was compared with Kaplan–Meier analysis, followed by a log-rank test. Continuous variables between the two patient groups were analyzed with Student's t test. Multivariate analyses were performed with a multiple logistic regression test. In all instances, a probability value of <0.05 was considered significant.

To ensure that the data could be pooled, the data were analyzed to determine whether the intergroup patient demographic characteristics, histories, hemodynamic status, and blood chemistry profiles were similar within and among the various treatment centers. No dissimilarities were found that would adversely bias the statistical analyses.

The analyses occasionally necessitated the comparison of data from a small number of patients. The smallness of this subset may have limited the validity of some of the statistical tests. In these cases, the ability to demonstrate differences was limited; nevertheless, the statistical tests were performed, so that we could draw the most accurate conclusions possible based on the data available.

RESULTS

Pretransplant And Early Posttransplant Survival

The average interval between enrollment into the study and either transplantation or death was 12 days (range, 1–72 days) for the control group and 76 days (range, <1–344 days) for the LVAS group. Twenty-one LVAS and 21 control patients died before they underwent transplantation. Thus, the pretransplant mortality of the LVAS group was 55% less than that of the control patients (p = 0.001).

Of the 75 LVAS patients, 53 (71%) underwent transplantation. Four died of donor heart failure less than 60 days after transplantation, and the remaining 49 (65%) were alive at 60 days (Table 3). In contrast, only 12 (36%) of the control patients underwent transplantation, and 2 died of posttransplant heart failure. The remaining 10 patients (30%) were alive at 60 days.

With respect to both transplantation rate and 60-day survival rate, the intergroup differences were significant (p = 0.001 for both variables).

One-Year Posttransplant Survival

More LVAS patients were alive at 1 year than control patients: 48 (91%) *versus* 8 (67%) (p = 0.0001). Using a life-table analysis, we compared the two groups' survival rates for the first year after transplantation (Fig. 2). The

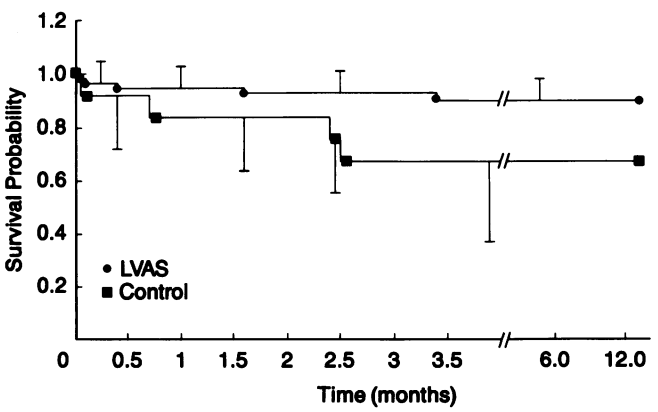

Figure 2. One-year posttransplant actuarial survival for the LVAS and control groups. The LVAS group had a 90% probability of survival, compared with a 67% probability for the control group (p = 0.0335). According to a log-rank test, the difference in the probability of survival was significant.

probability of 1-year survival was 90% for the LVAS group, compared with 67% for the control group. According to a log-rank test, this difference was significant ($p = 0.03$).

Hemodynamic Effectiveness

The HeartMate IP LVAS provided adequate long-term hemodynamic support, maintaining one patient for as long as 344 days. To confirm the device's effectiveness, we compared the average pump index (pump flow/body surface area) during LVAS support to the average baseline cardiac index (cardiac output/body surface area) obtained just before device implantation. The average pump index (2.77 L/minute/m^2) during LVAS support was **50% greater** than the corresponding baseline cardiac index (1.86 L/minute/m^2). The significance of this difference ($p = 0.0001$) was confirmed by a paired t test.

Most of the LVAS patients experienced significant improvement in renal and hepatic function during mechanical support. In the 53 patients who survived to transplantation, BUN and creatinine levels decreased significantly (Fig. 3), eventually returning to normal. However, in the 22 LVAS patients who did not survive to transplantation, renal function continued to deteriorate, presumably because of irreversible end-organ dysfunction that preceded LVAS implantation. In the 53 survivors, total bilirubin levels remained transiently elevated after LVAS implantation and then declined to normal (Fig. 4). In the 22 nonsurvivors, however, hepatic function deteriorated further.

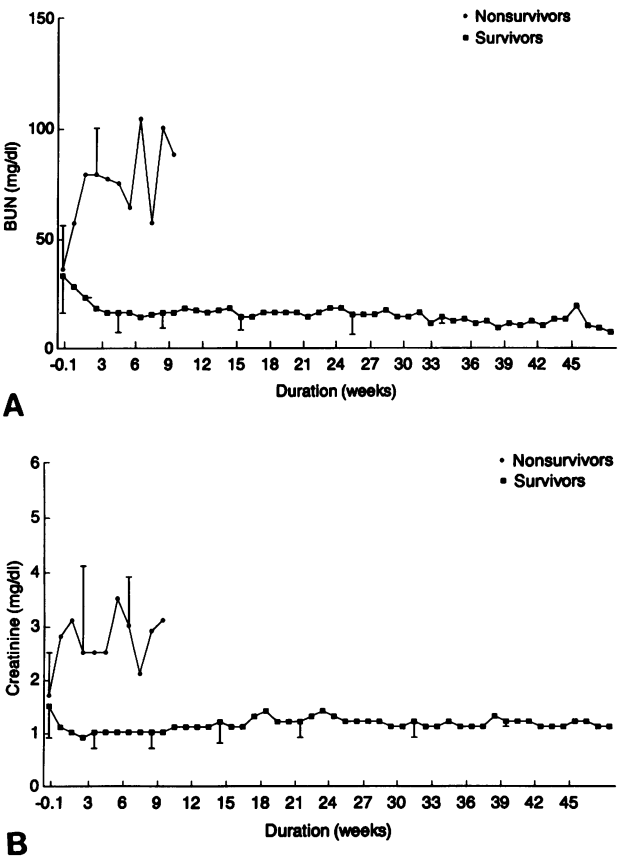

Figure 3. Most of the LVAS patients had improvements in renal function, as documented by changes in (A) BUN and (B) creatinine levels over time. These two levels returned to normal in the LVAS patients who survived to transplantation (survivors), but continued to increase in the patients who did not survive to transplantation (nonsurvivors), despite the restoration of blood flow.

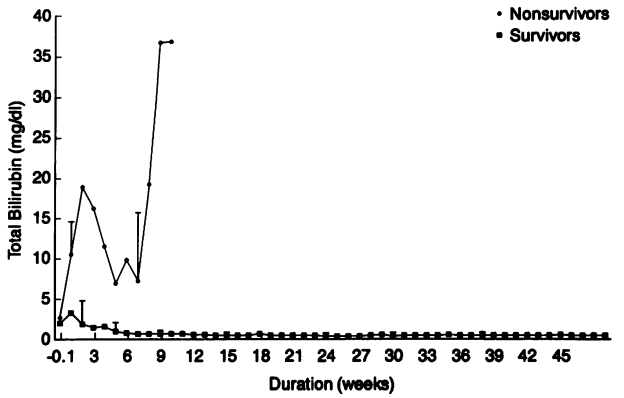

Figure 4. The LVAS survivors also had an improvement in hepatic function, based on a reduction in total bilirubin levels. In survivors, these levels increased transiently and then declined to normal. In the nonsurvivors, hepatic function continued to deteriorate despite the restoration of blood flow.

Although the LVAS performed satisfactorily in the nonsurvivors, these patients' end-organ function continued to deteriorate. A multivariate analysis of baseline parameters (including BUN, creatinine, total bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and cardiac index) failed to reveal any parameter, alone or in combination, that predicted nonsurvival. In addition, no single parameter predicted irreversible end-organ dysfunction. Thus, none of the factors analyzed during baseline studies predicted which patients would have irreversible end-organ dysfunction.

New York Heart Association Functional Status

During baseline studies before device implantation, 71 (95%) of the LVAS patients were in class IV, and the rest were in class III. Of the 53 patients who underwent transplantation, 48 (91%) were in New York Heart Association class I, and the remainder were in class II. Therefore, the LVAS produced a significant improvement in these patients' pretransplant functional capacity and quality of life.

Table 4. SUMMARY OF ADVERSE EVENTS

Event	LVAS Group (n = 75)	Control Group (n = 33)
Bleeding	31 (41)	0 (0)
Hemolysis	6 (8)	1 (3)
Infection	31 (41)*	5 (15)*
Right ventricular failure	11 (15)	1 (3)
Thromboembolism	3 (4)	0 (0)
Septic embolism	2 (3)	0 (0)
Renal dysfunction	40 (53)	20 (61)

Values are no. (%).
* According to Fisher's exact test, this difference was statistically significant ($p < 0.05$).

Effectiveness of the Textured Blood-Contacting Surfaces

After LVAS explantation, morphologic and biochemical analyses of the blood-derived biologic linings typically revealed a heterogeneous surface colonized by a variety of cell types. The majority of cells appeared to be macrophages; however, endothelial cells have been identified both histologically and immunochemically.[18] Other areas rich in collagen were also observed.[19]

As noted below, 3 (4%) of the 75 LVAS patients had a thromboembolic complication. Two additional patients (2.7%) had septic emboli. This low rate of embolic complications may be related to the textured blood-contacting surfaces of the HeartMate IP LVAS.

Adverse Events

Adverse events were summarized and analyzed for the LVAS and the control patients (Table 4).

Bleeding. As stated above, bleeding was monitored only in the LVAS group. Of these patients, 31 (41%) experienced bleeding. In nine patients (12%), bleeding was related to the device, originating from connectors, anastomoses, or needle holes that had been surgically created to evacuate air at the time of implantation. In the remaining 22 patients, bleeding was unrelated to the device but necessitated that the patient be returned to the operating room. No significant differences in transplantation ($p = 0.198$) and survival ($p = 0.198$) rates were found between the patients who did bleed and those patients who did not bleed (Fisher's exact test).

Hemolysis. During LVAS support, the plasma-free hemoglobin levels averaged 6.5 mg/dL, and the hemoglobin concentrations averaged 11.2 g/dL. Of the LVAS patients, six (8%) exhibited hemolysis, compared with one (3%) of the control patients ($p > 0.05$).

In two of the six LVAS patients, hemolysis occurred after cardiopulmonary bypass. In two other patients, elevated plasma-free hemoglobin levels occurred while the patients were undergoing concurrent treatment with a centrifugal blood pump for right ventricular failure. The fifth patient was undergoing hemodialysis when hemolysis occurred, and the sixth patient had two consecutive elevated plasma-free hemoglobin levels but remained asymptomatic. In the LVAS group, the transplantation and survival rates were significantly lower for patients with hemolysis (17% and 17%) than for those without hemolysis (75% and 75%) ($p = 0.007$), reflecting severity of illness in this subgroup of patients.

Right Ventricular Failure. In 11 (15%) of the LVAS patients, the right ventricle was incapable of delivering sufficient flow to the left ventricle during the perioperative period. In comparison, only one (3%) of the control patients had right ventricular failure. In each instance, a right ventricular assist device was used to maintain adequate flows. The incidence of right ventricular failure was not significantly different between the two groups ($p > 0.05$).

Only 1 (9%) of the 11 LVAS patients with right ventricular failure underwent transplantation and survived. In contrast, 52 (81%) of the 64 LVAS patients without such failure underwent transplantation and survived. Because this difference was significant ($p < 0.001$), right ventricular failure should be a contraindication for LVAS use.

Infection. The LVAS patients had significantly more infections ($n = 31$; 41%) than did the control patients ($n = 5$; 15%) ($p = 0.008$). This finding can be attributed to the fact that the LVAS patients underwent surgery, whereas the control patients did not, and the study duration (the time to transplantation) was significantly longer for the LVAS patients (average, 76 days) than for the control patients (12 days). Therefore, the LVAS patients had a longer exposure to risk ($p = 0.0001$).

Of the LVAS patients with infections, 25 (81%) underwent transplantation, and all 25 survived. When LVAS patients with and without infections were compared, no difference in overall outcome was found ($p = 0.13$).

Embolic Events. In the LVAS group, three patients (4%) had a thromboembolic complication during circulatory support. In the first instance, the origin of the thrombus was unclear; the patient, however, had a large, dilated native left ventricle, and the pump was free of thrombus at explantation. This patient required a subclavian artery thrombectomy, and he recovered fully, without residual neurologic dysfunction. He subsequently underwent transplantation and was discharged. In the second case, thrombus, which formed in the inflow conduit of the LVAS, appeared to have originated from the dilated native left ventricle. This patient

suffered a stroke and eventually died. The third patient had a stroke approximately 30 days after LVAS implantation. This complication was attributed to the release of thrombus from a mechanical aortic valve within the native heart, not to the device. This patient recovered, underwent transplantation after 173 days of LVAS support, and was later discharged from the hospital.

Two LVAS patients (2.7%) had septic emboli. One of these patients had undergone transplantation after 109 days of LVAS support. Nine days later, he had a visual disturbance. Examination of the LVAS outflow graft revealed a small vegetation consistent with *Candida* species. The visual disturbance may have been related to the release of a small embolus from the vegetation at the time of device removal. The second patient had a renal infarct after 111 days of LVAS support. This complication was also attributed to *Candida* vegetation on the pump. The patient subsequently had a cerebrovascular accident and died after 118 days of mechanical support.

Of the five patients who had a septic or thromboembolic event, three underwent transplantation and had minimal or no residual neurologic dysfunction. Three of the five patients (described above) had strokes, and two of them ultimately died of these sequelae.

Renal Dysfunction. After enrollment into the study, 40 (53%) of the LVAS patients and 20 (61%) of the control patients had renal dysfunction, as documented by creatinine levels of ≥2.2 mg/dL and/or BUN values of ≥50 mg/dL ($p > 0.05$). The difference in intergroup frequency of renal dysfunction was not significant. Of the LVAS patients, 32 (42%) had renal dysfunction before receiving the assist device.

In both groups, the survival rates were significantly lower for patients who had renal dysfunction at any time after enrollment. In the control group, only 16% of the patients with renal dysfunction survived, compared with 64% of those without such dysfunction ($p = 0.009$). Likewise, in the LVAS group, only 58% of the patients with renal dysfunction survived, compared with 86% of those without such dysfunction ($p = 0.01$). Although patients with renal dysfunction in both groups fared worse, survival for patients in the LVAS group was significantly better than that of the control patients ($p < 0.001$).

Additional Adverse Events. Other adverse LVAS-related events included bowel adhesions to the driveline in three patients, bowel perforation in two patients, and air emboli during implantation, with resultant neurologic dysfunction, in six patients.

In one patient, treated in 1988, loosening of an outflow connector after implantation of the blood pump necessitated a repeat operation to tighten the connector. Subsequently, the design was modified to incorporate a locking mechanism, and no additional adverse effects were observed. This is the only mechanical failure that we have encountered during 26 patient-years of experience with the HeartMate IP LVAS.

DISCUSSION

This study demonstrated significant (55%) reduction in mortality for patients awaiting heart transplantation who were treated with the HeartMate IP LVAS when compared with patients who were not treated with the system. Moreover, by improving these patients' renal and hepatic function as well as their physical capacity, LVAS support allowed them to be rehabilitated before undergoing transplantation. Compared with control patients, the LVAS patients had a significantly better survival rate 1 year after transplant. This result reflects the fact that the LVAS patients were in optimal condition at the time of transplantation.

Success in reducing the mortality of end-stage cardiac patients awaiting transplantation has not been limited to the HeartMate IP LVAS. Similar survival rates have been reported for other devices, such as the Novacor LVAS[13] and the Thoratec VAS.[20] Although these reports included no comparisons involving a control population, the collective results strongly support the effectiveness of ventricular assistance.

In our study, the nature and frequency of adverse events associated with the HeartMate IP LVAS were comparable to those reported for other devices. However, because our control patients did not undergo implantation of the LVAS, their time to death or transplantation was considerably shorter than the duration of implant in the LVAS patients. The study duration averaged 12 days for the control patients and 76 days for the LVAS patients. Consequently, the risk exposure time was six times longer for the LVAS patients.

According to previous reports, bleeding occurs in approximately 40% of LVAS-supported patients.[13,21] Our patients had a 41% incidence of bleeding after LVAS implantation. The use of aprotinin, introduced since this study was completed, appears, however, to be decreasing the incidence of this complication in these patients, most of whom have some form of coagulopathy related to their prolonged heart failure.

Infectious complications are more difficult to compare because of the manner in which the data are presented. Many patients have fever and positive cultures after routine postoperative cardiopulmonary bypass. Reported rates of infection range from approximately 20% to 75%, although not all infections have been device-related.[13,21,22] Our LVAS patients had a 41% incidence of infection, yet 81% of them underwent transplantation and survived. This indicates the difficulty in interpretation of this complication. Whereas mediastinal infection is the primary cause of death in 40% of the cases in which

the total artificial heart was used as a bridge to transplantation,[23,24] LVAS patients have a low incidence of fatal infections.[16,25]

In our study, right ventricular failure was identified as a significant adverse event. Approximately one of six LVAS patients died of such failure. In no instance, however, was it considered to be device-related. Because patients with right ventricular failure were less likely to undergo transplantation and survive, multiple retrospective analyses were performed to identify potential predictors of right ventricular failure before LVAS implantation, so that future high-risk patients could be screened out. Despite repeated attempts, we were unable to identify any such predictors. We did discover, however, that right ventricular failure and bleeding were associated. It is unclear whether bleeding was a cause of right ventricular failure or the result of treatment for such failure. Because of the apparent relationship between these two problems, however, bleeding during implantation must be minimized. Again, the use of aprotinin during implantation may help in these patients. Newer agents, such as nitric oxide, have also been shown to lower pulmonary vascular resistance, thereby reducing right ventricular failure.[26,27]

Although the incidence of thromboembolism has historically been of considerable concern,[28–30] the number of strokes related to embolic events was low (7%) in our LVAS group, despite the use of minimal anticoagulation. Of the three embolic events, two could be explained by the patients' native cardiac disease; the other was most likely related to the patient's native disease. The low incidence of embolism is attributed to the use of textured surfaces, which promote the *de novo* formation of a natural biologic lining. In addition, the excellent pump flow, characterized by a complete fill-to-empty pumping action, results in a complete washout of blood with each stroke.

Bridging to transplant was introduced in the 1980s as a treatment to save patients dying of end-stage disease while they awaited transplantation. As experience with bridges to transplant grew, it became obvious that survival of patients treated with an LVAS was better than survival of patients who waited for their transplants without such a device. In this study, 1-year survival for the LVAS patients was significantly greater when compared with survival of the control patients ($p = 0.001$). When the LVAS patients were compared with patients in the overall transplant population, their 1-year survival was also better; this finding has been confirmed by others.[13,31]

In addition, the costs associated with caring for the LVAS patients are actually much less than the costs for caring for their less healthy counterparts. As they progress to class I cardiac status, the LVAS patients are able to care for themselves. They can be transferred out of the intensive care unit to a regular floor, or, for some patients with the electrically powered model of this device, they can be discharged to wait for their transplants at home.[32] The care of patients in the intensive care unit awaiting transplant (and supported by an intra-aortic balloon pump) may be as high as $4000 per day.[14]

This study was limited by the fact that it was neither blinded nor randomized. We made every effort to avoid bias, however, by enrolling only those control patients who met the same entrance criteria as the LVAS patients, without our knowing the outcome. The patients had comparable hemodynamic and end-organ function at baseline study as well as similar histories and demographic data.

The ability to support the circulation artificially for extended periods has important implications for thousands of end-stage cardiac patients who fail to qualify for transplantation or for whom a donor heart is not available. According to recent estimates, 35,000 to 60,000 patients in the United States may be in need of mechanical circulatory support devices each year.[33] With only 2000 donor hearts available, transplantation fulfills only about 3% to 6% of this need. A reliable ventricular assist system may provide an acceptable alternative approach for end-stage heart patients with essentially no other options. On the basis of our favorable results to date, we are designing a study to evaluate the safety and effectiveness of the HeartMate LVAS as an alternative to conventional medical therapy for patients with congestive heart failure not otherwise eligible for a heart transplant.

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APPENDIX

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Discussion

DR. KEITH REEMTSMA (New York, New York): It is a pleasure for me to discuss this paper by Dr. Frazier and his colleagues. This work is an outstanding contribution to the important and evolving field of mechanical circulatory support.

This study demonstrates major changes both in concept and in technology since the earlier, much publicized work with the total artificial heart. The conceptual change involves the use of a mechanical device as an auxiliary or parallel pump rather than as a replacement for the heart, thus permitting the use of