Left ventricular assist device as bridge to transplantation does not adversely affect one-year heart transplantation survival

Joseph C. Cleveland, Jr, MD,^a Frederick L. Grover, MD,^a David A. Fullerton, MD,^a David N. Campbell, MD,^a Max B. Mitchell, MD,^a JoAnn Lindenfeld, MD,^b Eugene E. Wolfel, MD,^b Brian D. Lowes, MD,^b Simon F. Shakar, MD,^b Andreas Brieke, MD,^b Anne Cannon, RN, BSN,^a and Alastair D. Robertson, PhD^b

Objective: Left ventricular assist devices are increasingly used as a bridge to transplantation. It remains unclear whether the use of pretransplant left ventricular assist devices adversely affects short-term survival after cardiac transplantation.

Methods: A retrospective review of 317 consecutive patients undergoing cardiac transplantation at an academic center between 1986 and 2006 was undertaken. Left ventricular assist devices were used pretransplant in 23 of these 317 patients, and 294 patients did not require left ventricular assist device support. Patients with a left ventricular assist device were supported with a Heartmate VE or Heartmate XVE (Thoratec Corp, Pleasanton, Calif). Kaplan–Meier survival estimates were compared between the left ventricular assist device group and the non-left ventricular assist device group using the log-rank test. In addition, occurrence of death was analyzed between the 2 groups with a chi-square analysis. The results are expressed as 1-year survival with 95% confidence intervals in parentheses.

Results: The 1-year survival for all 317 patients was 0.86 (0.82–0.90). The patient survival for the group without a left ventricular assist device before cardiac transplant was 0.87 (0.83–0.90), and the survival for the group with a left ventricular assist device as bridge to transplantation was 0.83 (0.67–0.98; $P = .77$). For the deaths that occurred in all 317 patients, 19% of the patients without left ventricular assist devices died within 30 days of transplant, whereas 80% of the patients with left ventricular assist devices died within 30 days of transplant ($P < .01$).

Conclusion: When used as a bridge to transplantation, left ventricular assist devices do not compromise 1-year survival after cardiac transplantation. Of the patients who die after transplantation, patients bridged with left ventricular assist devices are at higher risk for death within 30 days of transplant. These data suggest that left ventricular assist devices as a bridge to transplantation should be considered for appropriately selected patients awaiting cardiac transplantation.

Cardiac transplantation is the accepted therapy for the treatment of end-stage heart failure. Indeed, because of the widespread application and success of cardiac transplantation, the need for more hearts than could be supplied by suitable donors rapidly developed. With potential heart transplant recipients dying on waiting lists because of a supply–demand imbalance for organs, the incentive to develop a reliable mechanical circulatory support device ensued. Portner and

From the Department of Surgery, Division of Cardiothoracic Surgery,^a and Department of Medicine, Division of Cardiology,^b University of Colorado at Denver and Health Sciences Center, Denver, Colorado.

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Address for reprints: Joseph C. Cleveland Jr., MD, Associate Professor of Surgery, Surgical Director Cardiac Transplantation and MCS, Division of Cardiothoracic Surgery, University of Colorado at Denver and Health Sciences Center, Academic Office 1, L15, 12631 E. 17th Ave, C310, PO Box 6511, Aurora, CO 80045 (E-mail: joseph.cleveland@uchsc.edu).

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Abbreviations and Acronyms

LVAD = left ventricular assist device

colleagues¹ reported the first successful cardiac transplant after bridging with a left ventricular assist device (LVAD) at Stanford University. This remarkable clinical milestone opened a new option for patients with decompensated heart failure who might otherwise die while awaiting transplantation. The use of an LVAD as a bridge to transplantation is now accepted for patients listed for transplant whose conditions deteriorate before a donor heart becomes available.^{2,3}

In the past, the use of a pretransplant LVAD was a risk factor for death after cardiac transplantation.⁴ However, 2 recent reports^{5,6} from separate transplant centers indicate that patients can be successfully bridged to transplant with an LVAD with equivalent outcomes to patients undergoing transplantation in these centers without LVAD placement. These reports now question whether pretransplantation LVAD use adversely affects short- and long-term survival after cardiac transplantation. We evaluated our center's 1-year post-cardiac transplant survival in patients undergoing transplantation with the support of the Heartmate VE or XVE LVAD (Thoratec Corp, Pleasanton, Calif) and in patients undergoing transplantation without LVAD support to determine whether LVAD implantation adversely affected 1-year survival.

Materials and Methods

We retrospectively reviewed 317 consecutive patients undergoing cardiac transplantation at the University of Colorado Health Sciences Center from 1986 to 2006. Pretransplant LVADs were placed in 23 of these 317 patients (LVAD group). The criteria for placement of an LVAD included patients with end-stage heart failure whose conditions deteriorated clinically while listed for heart transplantation despite inotropic or intra-aortic balloon counterpulsation support. At the University of Colorado Health Sciences Center, we initiated the bridge-to-transplant program with the Heartmate VE LVAD in October of 2000. The patients included in the present analysis represented all patients who underwent planned LVAD placement after a joint decision by the attending cardiothoracic surgeon and heart failure cardiologist. We excluded any patients with acute decompensation or a fulminant presentation who required extracorporeal membrane oxygenation or placement of a Thoratec ventricular assist device or Abiomed system (Abiomed, Danvers, Mass) as a bridge to either transplant or another device. In total, 28 patients underwent LVAD placement for bridge to transplant. The Heartmate VE LVAD was used in 10 patients, and the Heartmate XVE LVAD was used in 18 patients. No pretransplant LVAD support was used in 294 patients (NO LVAD group). This study received approval from the Colorado Multiple Institutional Review Board.

Immunosuppression posttransplant consisted of a calcineurin inhibitor (cyclosporine or tacrolimus), an antiproliferative agent (mycophenolate mofetil or azathioprine), and corticosteroids. The routine use of induction therapy with antithymocyte globulin or

OKT3 was not used; however, the use of lymphocytic agents was used only if renal function was compromised after transplant.

Demographic variables were compared between the 2 groups with the Student *t* test. Kaplan–Meier survival estimates were compared between the LVAD and NO LVAD groups with the log-rank test. The occurrence of death was also analyzed between groups with a chi-square analysis. The primary end point for this study was 1-year survival after transplantation.

Results

Pretransplant demographic and other clinical variables showed differences between the 2 groups (Table 1). In general, the patients in the LVAD group were younger and had greater body mass index, and the total graft ischemic time was longer in the LVAD group compared with the NO LVAD group. The percentage of patients with diabetes was similar between 2 groups, whereas the use of inotropes at the time of transplant was lower in the LVAD group. Although serum creatinine at the time of transplant was lower in the LVAD group, this value did not reach significance. Two patients with an LVAD who died early (<30 days) underwent transplantation with a documented device infection; none of the other 21 patients had clinical evidence of infection. Of the 28 patients with LVADs placed as bridge to transplant, 5 died after LVAD explantation while awaiting a donor heart (1 anoxic brain injury, 3 multiple systems organ failure, and 1 sudden cardiac death at home on day 71 of support). Thus, 23 patients comprised the LVAD group who underwent transplantation.

The 1-year survival was 82% for the LVAD group (Figure 1) and 87% for the NO LVAD group (Figure 2)

TABLE 1. Baseline demographics and clinical characteristics

	LVAD (n = 23)	NO LVAD (n = 294)	P value
Age (y)	45 ± 12	52 ± 12	<0.05
Cardiac diagnosis (%)			<0.05
Ischemic	55	32	
Dilated	36	47	
Other	9	21	
BMI	29 ± 5	25 ± 5	<0.05
Gender (M/F)	77%/23%	82%/18%	NS
Diabetes mellitus (%)	18	18	NS
Duration mechanical support (d)	165 ± 122	-	-
Inotrope use (at time of transplant) (%)	5	24	<0.05
LVEF (at listing) (%)	17 ± 5	22 ± 6	<0.05
Creatinine mg/dL (at transplant)	1.2 ± 0.5	1.4 ± 0.5	0.2
Ischemic time (min)	245 ± 60	175 ± 61	<0.05

LVAD, Left ventricular assist device; BMI, body mass index; LVEF, left ventricular ejection fraction; NS, not significant. Values are presented as mean ± standard deviation.

Figure 1. Kaplan–Meier survival analysis for 294 patients in the NO LVAD group after cardiac transplant is 0.87 with 95% confidence interval of 0.83 to 0.90.

Figure 2. Kaplan–Meier survival analysis for 23 patients in the LVAD group after cardiac transplant is 0.83 with 95% confidence interval of 0.67 to 0.98.

($P = .77$). For the 120 deaths that occurred in the entire group of 317 patients after transplantation, 19% of the NO LVAD group died within 30 days of transplant, and 80% of the LVAD group died within 30 days of transplant ($P < .01$). One-year survival after transplantation in the entire group of 317 patients is 87%.

With regard to specific causes of death, there were 4 deaths within 30 days in the LVAD group. Two patients died of early graft failure (right ventricular dysfunction in 1 patient and global graft dysfunction in 1 patient). One patient died of a cardiovascular accident/brain injury, and 1 patient died of multiple organ failure at 3 weeks (predominantly liver/infectious causes). The remaining death in the LVAD group occurred at 2.5 years posttransplant. In contradistinction, the NO LVAD group sustained 23 deaths within the first 30 days (7% early mortality). A total of 13 of the 23 deaths were caused by graft failure. This group included some of our earliest patients who underwent transplantation. Four deaths were secondary to brain injury/cardiovascular accident, 1 death was due to a severe acute rejection, 2 deaths had infectious-related causes, and 3 deaths were due to bleeding complications. The remaining 15 deaths occurred between 30 days and 365 days posttransplant, with more than half (9/15) related to infectious causes, 2 rejections, 1 anoxic brain injury, 1 sudden death (presumed graft failure), and 2 related to multiple organ failure/failure to thrive.

Discussion

LVAD therapy has been accepted as a viable strategy to bridge patients safely to transplantation. The impact of pre-transplantation LVAD on posttransplantation outcomes, however, is variable. Until recently, results from the International Society for Heart & Lung Transplantation database suggested that the presence of an LVAD at the time of transplantation conferred an adverse risk for 1-year mortality. The perception among most transplantation centers is that explantation of an LVAD confers a more technically challenging

operation and therefore might adversely affect survival. Indeed, the ischemic time for the donor heart from the LVAD group was significantly longer than the ischemic time in the NO LVAD group, which likely reflected the complexity involved in explanting the LVAD (Table 1).

In the present study, we observed excellent and comparable 1-year survival after heart transplantation in both the LVAD and NO LVAD groups. No survival decrement existed for the LVAD group at 1 year after transplantation. An important distinction, however, remains on the timing of death after transplantation between the 2 groups. For patients who die after transplantation, most of the LVAD group (80% of deaths after transplant in this group) died within 30 days of transplant. In contrast, a minority of the patients without an LVAD died within 30 days of transplantation. It remains likely that this pattern of death after transplantation reflects the inherent complexity and higher risk operation that occurs with explantation of an LVAD at the time of transplantation. Also, 2 of the 4 patients in the LVAD group who died early after transplantation had clinical evidence of device infection at the time of transplantation. One of these 2 patients underwent transplantation very early after his LVAD implantation, and our program now strongly avoids early (<30 days since LVAD placement) device explantation and transplantation. Our preference is to defer transplant in our LVAD group until patients are ambulatory and nutritionally replete, and have demonstrated end-organ recovery from decompensated heart failure and subsequent physiologic stress after LVAD implantation. The other causes of death in the remaining 2 patients were graft dysfunction and severe neurologic injury. Although the NO LVAD group sustained more than half of their early deaths secondary to graft dysfunction, the details remain difficult to define in this retrospective study. Many of these deaths occurred earlier in the transplantation group, in the first years of our program, and may reflect differential expertise with donor management, greater experience with recipient management, and overall

improved outcomes with center experience. The inherent confounding differences between the LVAD group and the NO LVAD group that certainly exist in this retrospective study may account for this differential early mortality.

Two other centers with extensive LVAD as bridge to transplantation experience recently reported results similar to the present study. Morgan and colleagues,⁶ at Columbia Presbyterian, reported their experience with the Heartmate LVAD for a 12-year period. They noted no difference in 1-year survival after transplantation with an LVAD versus those patients without an LVAD. They noted an incremental improvement in patients' survival as they transitioned from the Heartmate IP to the Heartmate VE to the Heartmate XVE device. It can be argued, however, that their improvement in survival was a function of incremental experience with the LVAD as a bridge to transplantation rather than attributes of the device. Drakos and colleagues,⁵ from the Utah Transplantation Affiliate Hospitals, reported similar 1-year survival after transplant in patients with an LVAD (85%) versus those without an LVAD (92%). Both of these studies were also retrospective reports.

Our study differs from these previously reported studies, in that the Drakos study included 2 devices: the Heartmate and the CardioWest Total Artificial Heart (SynCardia Systems Inc, Tucson, Ariz). Our study included only patients who underwent transplantation with a Heartmate LVAD and, most important, reflected our "learning curve" as we initiated our Heartmate LVAD program in 2000. We included every patient who underwent transplantation with a Heartmate LVAD since we began using this device in our program. Thus, although both the Columbia and Utah Transplantation Affiliate Hospitals reports represent larger volume centers with a greater cumulative experience than most programs, the present study reports similar outcomes in a program with modest experience and reflects our initial and most recent implant successes and failures. Our outcomes in this study reflect the increasingly observed effect of patient selection as a critical determinant of post-LVAD survival. We did not include patients who had such an acute decompensation that they manifested irreversible end-organ damage after LVAD placement.

Several limitations of the present study must be considered. First, this study is retrospective. Inherent bias, such as selection of patients for an LVAD as a bridge to transplantation, is a legitimate criticism. The use of historical controls to compare the LVAD cohort with the non-LVAD cohort introduces confounding effects of other therapies in the more recent transplant recipients as an uncontrolled variable that could improve the results in the LVAD cohort. Countering this argument is the observation that our overall transplant 1-year survival has remained stable at 87% for several years in our program. The small number of the LVAD group analyzed relative to the larger cohort may have resulted in a type II statistical error, which accounted for our lack of difference

in 1-year survival. Our report is from a single center with modest transplant and LVAD volumes. As such, we would still advocate that other cumulative experience, such as the International Society for Heart & Lung Transplantation database or outcomes from the INTERMACs database, might provide a much more comprehensive composite experience from the transplant and LVAD community. We did not compare the survival of the NO LVAD group to transplantation with the 28 patients who originally received LVADs. Because 5 patients in the LVAD group died while awaiting transplantation, we elected to begin the analysis with the 23 patients who survived until transplant. We did not have reliable data to compare the survival of the NO LVAD group at the time of listing with the LVAD group at the time of listing. Thus, the current study must be interpreted with this caveat.

Conclusions

Our data suggest that the use of an LVAD as a bridge to transplantation does not compromise 1-year survival after cardiac transplantation. In patients who died after transplantation, there is a differential timing of death after transplantation in patients with an LVAD. The LVAD group sustained death very early after transplant (within 30 days) compared with the NO LVAD group. The challenges of transplants with an LVAD as a bridge to transplantation remain, and we would still maintain that the explantation of an LVAD followed by transplantation is a technically challenging operation. However, our data suggest that appropriately selected patients for an LVAD as a bridge to transplantation fare as well as their non-LVAD counterparts. These data continue to support the judicious use of an LVAD as a bridge to transplantation and demonstrate that even in centers with a modest experience, good outcomes for transplantation after LVAD can be achieved.

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