Postcardiac transplant survival in the current era in patients receiving continuous-flow left ventricular assist devices

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Objectives: Continuous-flow left ventricular assist devices have become the standard of care for patients with heart failure requiring mechanical circulatory support as a bridge to transplant. However, data on long-term post-transplant survival for these patients are limited. We evaluated the effect of continuous-flow left ventricular assist devices on postcardiac transplant survival in the current era.

Methods: All patients who received a continuous-flow left ventricular assist device as a bridge to transplant at a single center from June 2005 to September 2011 were evaluated.

Results: Of the 167 patients who received a continuous-flow left ventricular assist device as a bridge to transplant, 77 (46%) underwent cardiac transplantation, 27 died before transplantation (16%), and 63 (38%) remain listed for transplantation and continued with left ventricular assist device support. The mean age of the transplanted patients was 54.5 ± 11.9 years, 57% had an ischemic etiology, and 20% were women. The overall mean duration of left ventricular assist device support before transplantation was 310 ± 227 days (range, 67-1230 days). The mean duration of left ventricular assist device support did not change in patients who had received a left ventricular assist device in the early period of the study (2005-2008, n = 62) compared with those who had received a left ventricular assist device later (2009-2011, n = 78, 373 vs 392 days, P = NS). In addition, no difference was seen in survival between those patients supported with a left ventricular assist device for fewer than 180 days or longer than 180 days before transplantation (P = NS). The actuarial survival after transplantation at 30 days and 1, 3, and 5 years by Kaplan-Meier analysis was 98.7%, 93.0%, 91.1%, and 88.0%, respectively.

Conclusions: The short- and long-term post-transplant survival for patients bridged with a continuous-flow left ventricular assist device in the current era has been excellent. Furthermore, the duration of left ventricular assist device support did not affect post-transplant survival. The hemodynamic benefits of ventricular unloading with continuous-flow left ventricular assist devices, in addition to their durability and reduced patient morbidity, have contributed to improved post-transplant survival. (J Thorac Cardiovasc Surg 2013;145:575-81)

Cardiac transplantation remains the reference standard for the treatment of patients with end-stage heart failure, although its widespread application has been limited by the insufficient pool of suitable donors.[1] The discrepancy between the limited availability of donor hearts and the increasing number of patients with heart failure whose condition deteriorates while on the heart transplant waiting list or who have advanced heart failure with end-organ dysfunction at listing has led to the increasing use of left ventricular assist devices (LVADs) as a bridge to transplant (BTT). Thus, the use of LVADs as a BTT has evolved to become the standard of care in most cardiac transplant programs.[2-4] The outcomes with mechanical circulatory support have gradually improved over time owing to improvements in device technology, the experience gained in intraoperative and perioperative patient management, and attention to patient selection and timing of LVAD implantation.

More recently, continuous-flow devices have rapidly become the standard of care when used as a BTT, with excellent outcomes reported.[5,6] However, limited data have been reported on the post-transplant survival of patients supported by continuous-flow devices. Thus, concern regarding the effect of an additional surgical procedure on outcomes remains. This is an important question because conflicting reports have been published on the effect of LVADs on post-transplant survival.[7-11] The objective of the present study was to evaluate the post-transplant survival of patients supported by continuous-flow devices at a single center.

METHODS

Patients

We evaluated all patients who received a continuous-flow LVAD as a BTT from June 2005 through September 2011 at the University of Minnesota Medical Center. Patients who received LVAD as destination

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Abbreviations and Acronyms

BMI = body mass index
BTT = bridge to transplant
INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support
LVAD = left ventricular assist device
UNOS = United Network for Organ Sharing

therapy or device exchange for failing pulsatile pumps were excluded. We identified 167 patients. Of these patients, 77 had received orthotopic heart transplantation after continuous-flow LVAD support during the study period. The present study focused on these 77 patients who had undergone heart transplantation after implantation of a continuous-flow LVAD.

LVADs Used

The continuous-flow LVADs included in the present study included HeartMate II (Thoratec Corp, Pleasanton, Calif), VentrAssist (Ventracor, Brisbane, Australia), and HVAD (HeartWare, Framingham, Mass). The details of the devices and their surgical implantation have been previously described.[5,12,13]

Data Collection

After the patients had provided written informed consent, we collected the baseline and follow-up data, including patient characteristics, body mass index (BMI), blood type, chemistry panel results, and hemodynamic parameters. After the patients were discharged from the hospital, they returned to the University of Minnesota Medical Center for follow-up, device review, and general status assessment.

Device Management

All patients were receiving standard heart failure therapy, including antiarrhythmic therapy, as per our usual practice. Anticoagulation involved a combination of warfarin and aspirin. The defibrillator or biventricular pacing settings were not changed after LVAD placement. All patients underwent a standard postoperative rehabilitation program.

Post-Transplant Follow-up

After transplantation, the patients were followed up on a routine basis. Survival after transplantation was determined at 30 days and 1, 3, and 5 years. The patients were also stratified by the duration of LVAD support (>180 or <180 days of LVAD support), age, gender, BMI, etiology, and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile. The mean duration to transplantation by era (early 2005-2008 and current 2009-2011) included patients who had undergone transplantation and those awaiting transplantation. Those patients awaiting transplantation were analyzed in the era in which they had received the LVAD and were censored for the end of the study period.

Immunosuppression

A standard heart transplant immunosuppression protocol was implemented at our center and was applied to all patients throughout the study period. In patients with normal renal function, mycophenolate mofetil 1500 mg twice daily, tacrolimus 1 to 2 mg twice daily, and a 1-mg/kg initial dose prednisone taper were initiated. The prednisone taper was typically completed within 4 to 6 months after transplantation. If the patient had renal dysfunction (glomerular filtration rate <30 mL/min/1.73 m^2) for 3 days after transplantation, an interleukin-2 receptor antagonist was used (daclizumab was preferred until unavailable owing to product discontinuation, with basiliximab used currently). The tacrolimus trough levels were routinely monitored, and the tacrolimus dose was adjusted to maintain a therapeutic level, determined by the duration since transplantation.

Statistical Analysis

We prospectively collected and retrospectively analyzed all the data. Continuous data are presented as the mean ± standard deviation. Categorical data are presented as percentages. Continuous data were compared using analysis of variance or the *t* test, as indicated. The chi-square test or the Fisher exact test was used for categorical variables. Survival estimates were determined using the Kaplan-Meier method and compared using log-rank statistics. All analyses were done using SPSS, version 12.0, software (SPSS, Chicago, Ill).

RESULTS

Patient Characteristics

A total of 167 patients received a continuous-flow LVAD as BTT during the study period at the University of Minnesota Medical Center. Of these patients, 77 underwent cardiac transplantation (46%), 27 died before transplantation (16%), and 63 (38%) remained listed for transplantation with ongoing LVAD support. A comparison of the baseline characteristics of the transplanted LVAD patients and those BTT patients who still required LVAD support demonstrated that the transplanted patients were older (54.5 ± 12 vs 48 ± 14 years, $P = .006$) and had a shorter duration of LVAD support (310 ± 227 vs 498 ± 370 days, $P = .017$). No significant difference was found in gender, BMI, blood type, or etiology between the transplanted LVAD patients and those continuing with LVAD support. The baseline characteristics of the transplanted patients versus those BTT patients who continued with LVAD support are listed in Table 1.

The mean age of the transplanted patients was 54.5 ± 12 years (range, 17-71 years). Most patients were men (n = 62, 80.5%). The etiology of heart failure in these patients was ischemic in 44 (57%), nonischemic in 29 (38%), and other in 4 (5%). Of the 77 patients, 55 received the HeartMate II LVAD, 19 received the VentrAssist, and 3 received the HVAD. Most patients were overweight, with a mean BMI of 29 kg/m^2. Most patients had blood group A (43/77, 55.8%). The baseline demographic characteristics of these 77 patients are summarized in Table 2.

TABLE 1. Comparison of baseline characteristic

Variable	Transplanted patients (n = 77)	Continued with LVAD support (n = 63)	*P* value
Ischemic etiology	44 (57%)	26 (41.2%)	.056
Male gender	62 (80.5%)	44 (69.8%)	.095
Age*	54.5 ± 12	48 ± 14	.006
BMI (kg/m^2)	29 ± 5.5	29.3 ± 7.8	.057
LVAD duration*	310 ± 227	498 ± 370	.017
Blood type			.083
A	43	22	
B	5	5	
AB	1	1	
O	26	34	

LVAD, Left ventricular assist device; *BMI,* body mass index. *$P < .05$.

TABLE 2. Baseline demographic characteristics of patients bridged to transplant with continuous-flow LVAD (n = 77)

Variable	Value
Age (y)	
Mean ± SD	54.5 ± 12
Range	17-71
Male gender	62 (80.5)
Etiology	
Ischemic	44 (57)
Nonischemic	29 (38)
Other	4 (5)
LVAD	
HeartMate II	55
VentrAssist	19
HVAD	3
Duration of support (d)	
Mean ± SD	310 ± 227
Range	67-1230
BMI (kg/m^2)	29 ± 5.6
Blood type (n = 75)	
A+	36
A−	7
AB+	1
B+	5
O+	22
O−	4
INTERMACS profile	
1	12
2	9
3	9
4	16
5	22
6	9
Renal function	
Sodium	135 ± 5
Creatinine	1.4 ± 0.6
BUN	33 ± 20
Liver function	
ALT	81 ± 236
AST	80 ± 224
Total bilirubin	1.15 ± 1.0

Data presented as mean ± standard deviation, n (%), or n. *LVAD,* Left ventricular assist device; *BMI,* body mass index; *INTERMACS*, Interagency Registry for Mechanically Assisted Circulatory Support; *BUN*, blood urea nitrogen; *ALT,* alanine aminotransferase; *AST,* aspartate aminotransferase; *SD*, standard deviation.

TABLE 3. Baseline and pretransplant hemodynamics

Variable	Pre-LVAD baseline hemodynamics	Pretransplant hemodynamics	*P* value
Systolic blood pressure (mm Hg)	108 ± 18.4	108 ± 18	.256
Diastolic blood pressure (mm Hg)	70 ± 11.2	81 ± 14	.057
Right atrial pressure (mm Hg)*	12 ± 6	7 ± 5	.001
Pulmonary artery systolic pressure (mm Hg)*	55 ± 14	35 ± 12	<.001
Pulmonary artery diastolic pressure (mm Hg)*	26 ± 9	15 ± 7	<.001
Mean pulmonary artery pressure (mm Hg)*	37 ± 9	22.5 ± 9	<.001
Cardiac index (L/min m^2)*	2.0 ± 0.5	2.4 ± 0.4	<.001
Cardiac output (L/min)*	4.2 ± 1	4.9 ± 1	.002

LVAD, Left ventricular assist device. *P < .05.

Hemodynamics

The baseline hemodynamics and pretransplant hemodynamics for these LVAD patients are listed in Table 3. Significant improvement was seen in the right atrial pressure, pulmonary artery pressures, and cardiac output and index among these patients with LVAD support.

Post-Transplant Outcomes

Time to transplantation. The 77 transplanted patients had a mean duration to transplantation after LVAD support of 310 ± 227 days (range, 67-1230 days). The mean duration to transplantation according to the INTERMACS profile was 343 ± 297 days for INTERMACS 1 (crash and burn, n = 12), 365 ± 284 days for INTERMACS 2 to 3 (inotrope dependent, n = 18), and 276 ± 178 days for INTERMACS 4 to 7 (ambulatory, n = 45; P = NS).

Of the 77 patients, 62 were treated in the early era (2005-2008), with a mean waiting time for transplantation of 373 ± 354 days, and 78 were treated in the current era (2009-2011), with a mean waiting time for transplantation of 392 ± 262 days (P = NS).

Transplantation for LVAD-related complications. Of the 77 patients who were transplanted, 5 (6.5%) were listed as United Network for Organ Sharing (UNOS) status 1A for LVAD-related complications. These included the need for inotropes in 2, frequent LVAD alarms with device malfunction in 2, and pump thrombus in 1. Only the patient with pump thrombosis died 87 days after heart transplantation of alveolar hemorrhage.

Of those patients who were initially implanted for BTT, 2 were excluded from the listing for transplantation because of LVAD-related complications. One patient had a cerebrovascular accident and the other developed severe bronchomalacia after LVAD implantation. These complications resulted in exclusion from transplantation and designation as destination therapy. In addition, a few patients were initially implanted with the intent for BTT but did not undergo transplantation because of other non-LVAD–related issues such as the development of malignancy or patient choice to continue with LVAD support.

Survival. The 30-day operative survival for the transplanted patients was 98.7%. The 1-, 3-, and 5-year survival by Kaplan-Meier analysis was 93.0%, 91.1%, and 88.0%, respectively (Figure 1).

The post-transplant 1-year survival data stratified by baseline demographics are listed in Table 4. No significant difference was seen in 1-year survival between patients with

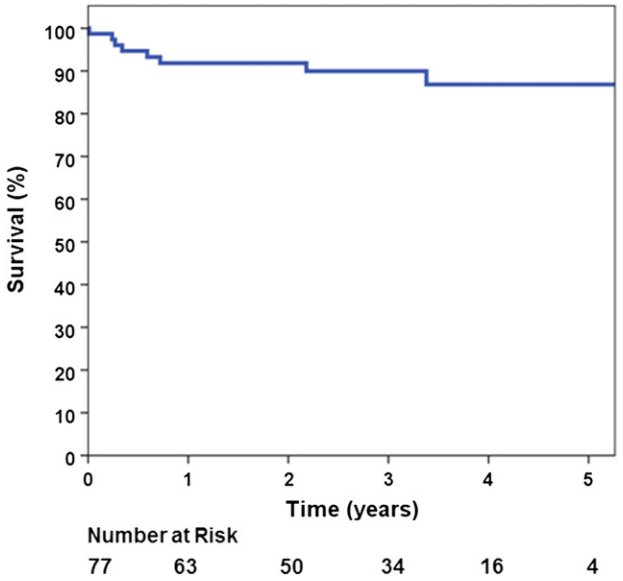

FIGURE 1. Survival by Kaplan-Meier estimate for post-transplant patients after continuous-flow left ventricular assist device implantation.

an ischemic or a nonischemic etiology (90.1% vs 93.2%, P = NS). No difference was seen in 1-year post-transplant survival between men and women (90% vs 100%, P = NS). In evaluating post-transplant survival at 1 year by age group, no significant difference was found among patients younger than 50, 50 to 59, or older than 60 years (100% vs 90.2% vs 92.9%, P = NS). Similarly, no difference was seen in survival between nonobese patients (BMI < 30 kg/m^2) and obese patients (BMI ≥ 30 kg/m^2; 95% vs 87%, P = NS). In addition, no difference was seen in 1-year survival between those patients supported with an LVAD for fewer than 180 days versus longer than 180 days before transplantation (88.5% vs 92.9%, P = NS). No difference was seen in 1-year-post transplant survival according to the INTERMACS profile (1 [crash and burn], 2-3 [ionotrope dependent], and 4-7 [ambulatory], 91.7%, 100%, and 88.6%, respectively; P = NS).

TABLE 4. Survival of post-LVAD transplant patients stratified by demographics

Demographic	Survival at 1 y	*P* value
Etiology		.89
Ischemic	90.1%	
Nonischemic	93.2%	
Gender		.152
Male	90%	
Female	100%	
Age (y)		.775
<50	100%	
50-59	90.2%	
>60	92.9%	
BMI (kg/m^2)		.196
<29.9	95%	
>30	87%	
LVAD duration (d)		.47
<180	88.5%	
≥180	92.9%	
INTERMACS profile		.26
1	97.1%	
2-3	100%	
4-7	88.6%	

LVAD, Left ventricular assist device; *BMI,* body mass index; *INTERMACS,* Interagency Registry for Mechanically Assisted Circulatory Support.

TABLE 5. Death of patients transplanted after LVAD

Age (y), gender	Etiology	Duration of LVAD support (d)	Transplant duration (d)	Cause of death
35, Male	Nonischemic	115	264	MSOF
65, Male	Ischemic	112	1232	Respiratory failure secondary to lung adenocarcinoma
52, Male	Ischemic	1129	125	Sepsis, MSOF
66, Male	Nonischemic	199	217	MSOF
51, Male	Ischemic	287	795	Cardiogenic shock secondary to antibody-mediated rejection
63, Male	Ischemic	487	97	Septic shock
62, Male	Nonischemic	67	87	Alveolar hemorrhage
53, Male	Ischemic	225	4	MSOF

LVAD, Left ventricular assist device; *MSOF,* multisystem organ failure.

Post-Transplant Deaths

One patient died 4 days after transplantation of multisystem organ failure. The other 7 deaths occurred 87 to 1232 days after transplantation. Only 1 death was secondary to antibody-mediated rejection. The median time to death in the transplanted patients was 212 days. The cause of death for these patients is listed in Table 5; the cause of death for the 27 patients who died after LVAD placement but before transplantation is listed in Table 6.

DISCUSSION

As mentioned, the discrepancy between the limited availability of donor hearts and the ever-increasing number of patients with heart failure has led to the increasing use of LVADs as a BTT. The therapeutic options and alternatives for these patients needing an LVAD are limited. The decision to delay LVAD implantation and to support a patient on the heart transplant waiting list with intravenous inotropic therapy is often determined by a shorter expected waiting time for a heart donor; the waiting time varies considerably across the United States according to blood group, body size, and other variables. In the current era, the success in terms of improved survival, reduced adverse events, and proven device durability reported for the current

TABLE 6. Cause of death of LVAD BTT patients (n = 27) who died before transplantation

Age, gender	Etiology	Support duration (d)	Cause of death
Early mortality (<30 d; n = 6)			
23, Male	Myocarditis	10	Subclavian vein hemorrhage
59, Male	Ischemic	15	MSOF, vasoplegic shock
46, Male	Ischemic	17	MSOF
53, Female	Ischemic	28	Ventricular fibrillation arrest
66, Male	Ischemic	30	MSOF
61, Male	Ischemic	30	MSOF
Late mortality (>30 d; n = 21)			
57, Male	Ischemic	32	MSOF
46, Female	Giant cell myocarditis	33	Transtentorial herniation from intraparenchymal bleeding
56, Male	Sarcoidosis	33	Withdrawal of care
54, Male	Ischemic	42	Device failure
67, Male	Nonischemic	73	MSOF
48, Male	Nonischemic	89	Respiratory failure, withdrawal of care
44, Male	Ischemic	92	MSOF, septic shock
60, Male	Ischemic	133	Cardiopulmonary arrest
70, Male	Ischemic	154	Pancreatic cancer
38, Male	Nonischemic	157	Unknown
47, Male	Ischemic	158	Unknown
61, Male	Ischemic	188	Withdrawal of care
44, Male	Ischemic	338	Respiratory failure
55, Male	Ischemic	355	Intraparenchymal cranial bleeding
61, Male	Ischemic	435	Intracranial hemorrhage
25, Female	TGA	500	MSOF
68, Male	Ischemic	560	Withdrawal of care
24, Female	Viral dilated cardiomyopathy	644	MSOF, sepsis
69, Male	Ischemic	1104	Withdrawal of care
49, Male	Ischemic	369	Methamphetamine overdose
34, Female	Nonischemic	1477	MSOF, sepsis

LVAD, Left ventricular assist device; *BTT,* bridge to transplant; *MSOF,* multisystem organ failure; *TGA,* transposition of great arteries.

generation of continuous-flow devices has all but eliminated the use of inotropes in most centers as an alternative to an LVAD as a BTT. The use of mechanical circulatory support as a BTT has evolved to become the standard of care in most cardiac transplant programs. Furthermore, although the results using LVADs as a BTT have been similar to those for patients transplanted without LVAD support, conflicting reports have been published on the effect of LVADs on post-transplant survival.[7-11] The findings from the present study support the increasing evidence that patients supported with continuous-flow LVADs have acceptable post-transplant survival. It appears that the excellent hemodynamic, functional, and survival benefits afforded by continuous-flow LVADs are closely linked to the post-transplant survival benefits.[5,14]

The changes in the UNOS guidelines for heart organ sharing to prioritize the use of donors primarily for status 1A patients have had a significant effect on the use of LVADs for BTT. Patients who are status 1B are now much less likely to receive a donor heart, and patients who are status 2 rarely undergo heart transplantation. These changes, as well as the continued increases in waiting times, have contributed to the rapidly increasing use of LVADs.

Although the results with LVADs have consistently improved over time, several questions remain with regard to patient management and the optimal timing of cardiac transplantation after the initiation of LVAD support.[5,6] The decision to proceed with heart transplantation after the initiation of LVAD support is guided partly by variables not in full control of the transplant team, such as donor availability, the UNOS policy for listing, and patient-related variables such as blood group and body size. Ultimately, the decision to proceed with active listing lies with the transplant team, as does the decision to either accept or refuse a donor heart for the potential recipient. In recent years, significant UNOS policy changes affecting LVAD BTT candidates have occurred because of outcomes data from patients supported with pulsatile devices.[15] It is possible that additional changes will occur on the basis of waiting list and post-transplant survival outcomes for patients supported with the newer generation continuous-flow rotary devices.

The currently available data could have significant implications for changing the current UNOS criteria regarding the listing of LVAD BTT candidates. In the previous HeartMate XVE era, changes in UNOS policy significantly

affected the LVAD BTT candidates. Although additional data with longer term follow-up are essential to make definitive recommendations, the clinical outcomes data with continuous-flow devices might suggest whether stable patients with the HeartMate II device should be listed as UNOS status 1A in the absence of any LVAD-related complications. A recent study demonstrated that the stability achieved with implanted LVADs was much greater than can be achieved among other subgroups of patients listed as status 1A.[16] The current 30-day period allocated to LVAD patients listed as status 1A could result in competition between similarly listed patients but with very different risks of death (eg, patients with intra-aortic balloon pump support who might have a contraindication to an LVAD). A more equitable change might allow for a status IA listing for LVAD patients who have a device complication such as a persistent infection or recurrent arrhythmias or who have developed sensitization.[16,17]

The recent advent of continuous-flow LVADs has had an important effect on survival and quality of life of patients with advanced heart failure. Although steady improvements have been reported for continuous-flow devices, an important observation in a post-trial study was a decrease in the percentage of patients undergoing heart transplantation from the clinical trial to the post-trial periods.[18] After 6 months of LVAD support, 32% of patients had undergone transplantation in the trial compared with only 22% of the post-trial patients. Similarly, by 12 months, 48% of the trial patients had received a transplant compared with 39% of the post-trial patients. Not unexpectedly, the increased numbers of continuous-flow devices being implanted has led to increased competition for a limited number of donors, the major reason for the longer waiting time to transplantation. It remains unclear why an increased waiting time to transplantation was not found during the latter part of the present study.

When the clinical trials with continuous-flow devices began just over 1 decade ago, concern was expressed regarding the uncertainty of the long-term effects of systemic arterial blood flow with low pulsatility. However, the large amount of cumulative experience with continuous-flow devices (primarily the HeartMate II) has indicated that long-term support does not have obvious detrimental effects on organ function. More relevant to the present study is a recent report that a prolonged duration of support with continuous-flow devices might be associated with greater hemodynamic compromise, which was demonstrated by the need for greater dose requirements and increased duration of pressor support after restoration of pulsatility at transplantation.[19] Although the later study showed no differences in early post-transplant mortality compared with patients receiving pulsatile devices, some studies have noted differences in vascular tone and endothelial function in patients supported with continuous-flow devices.[20,21] Studies in animal models have shown that the hemodynamic consequences of long-term nonpulsatile flow include disruption of the renin-angiotensin system and an altered responses to norepinephrine administration. Other studies have shown histologic changes in arterial wall medial thickness and changes in smooth muscle and elastin content during continuous-flow device support.[22,23] Nevertheless, despite possible changes to vascular and endothelial function, patients supported with continuous-flow devices have had excellent outcomes after cardiac transplantation.

The durability and reliability of the LVAD design is, perhaps, 1 of the most significant features for continued extended use of mechanical circulatory support devices. Previous studies demonstrated limited durability and reliability for the pulsatile HeartMate XVE LVAD, with nearly 50% of patients experiencing device exchange because of infection or mechanical malfunction at 18 months.[24] Very few device replacements were required for device thrombosis, malfunction, or infection in the multicenter study or in our study. No mechanical failure of the device pumping mechanism was observed.[5,25] The absence of mechanical failure of the pumping mechanism is significant and has not been previously observed in trials evaluating older technology. The remarkable durability of the HeartMate II LVAD can allow for improved donor selection in contrast to the pulsatile pump era in which decreasing durability beyond the 1-year mark increased the urgency for transplantation and the subsequent potential for suboptimal donor selection.

Study Limitations

Our single-center study was limited to a relatively smaller number of patients compared with a multicenter study and included 3 different types of continuous-flow devices. Although recently published multicenter data have shown evidence of the excellent post-transplant outcomes for patients with continuous-flow devices, the strength of the present study was the large number of patients undergoing implantation at a single center with consistent perioperative and postoperative management strategies. In addition, donor selection and recipient listing algorithms are more likely to be uniform at a single center. Although multicenter studies do have strict inclusion and exclusion criteria and guidelines for perioperative management, it is clear that multiple areas exist for investigators to use strategies that often differ at individual centers. Other limitations of the present study included the lack of data on post-transplant morbidity, such as rejection and infection.

In conclusion, the short- and mid-term post-transplant survival of patients supported by continuous-flow LVADs appears similar to the outcomes for non-LVAD BTT patients. In addition, no differences were seen in survival among transplanted patients when stratified by etiology of heart failure, gender, age, BMI, or duration of LVAD support. There is no reason, therefore, to support a hypothesis that the reduced pulsatility during LVAD support adversely

affects post-transplant survival. Our single-center data add to the increasing body of evidence that post-transplant survival for patients supported by continuous-flow devices is excellent and supports the current standard of care that continuous-flow devices are the primary therapeutic option for patients with advanced heart failure.

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