Long-term outcome of patients on continuous-flow left ventricular assist device support

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Objectives: Recent advances in technology and improved patient management have enabled the use of mechanical circulatory support for unexpected long-term periods. Improved long-term outcomes may facilitate the use of device therapy as an alternative to heart transplantation. However, there are scarce data about the long-term outcomes of continuous-flow left ventricular assist devices. This study sought to evaluate the long-term outcomes in patients receiving continuous-flow left ventricular assist devices.

Methods: Between March 2004 and June 2010, 140 patients underwent continuous-flow left ventricular assist device insertion as a bridge to transplantation or a destination therapy. These patients' charts were retrospectively reviewed.

Results: The initial strategy for continuous-flow left ventricular assist device therapy was bridge to transplantation in 115 patients (82%) and destination therapy in 25 patients (18%). Of those, 24 (17%) died on left ventricular assist device support, 94 (67%) were successfully bridged to transplantation, and 1 (0.71%) showed native heart recovery. Twenty-four patients (17%) had been on continuous-flow left ventricular assist device support for more than 3 years (mean, 3.9 years; range, 3.0-7.5 years). Estimated on-device survival at 1, 3, and 5 years was 83%, 75%, and 61%, respectively. Rehospitalizations due to bleeding, cardiac events, and device-related issues were common. The freedom from rehospitalization rates at 1 and 3 years was 31% and 6.9%, respectively. A total of 14 patients (10%) required device exchange.

Conclusions: Current continuous-flow left ventricular assist devices can provide satisfactory long-term survival. However, rehospitalization is frequently required. (*J Thorac Cardiovasc Surg* 2014;148:1606-14)

Continuous-flow left ventricular assist devices (CF-LVADs) have become an essential therapeutic option in the standard of care for patients with end-stage heart failure.¹ Clinical outcomes continue to improve through better patient selection, surgical techniques, and perioperative management.^{2,3} Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) data showed that 1- and 2-year survival in patients receiving these devices reach 80% and 70%, respectively.⁴ These favorable midterm results encourage the use of CF-LVADs both as a bridge to transplantation (BTT) and as a destination therapy (DT). The number of DT implants, as a permanent therapy, dramatically increased to more than 40% of the total LVAD implants in the United States in 2012.⁴

For BTT, because of the persistent donor organ shortage, the wait time on the device support for cardiac

transplantation has increased,⁵ and in clinical settings, we occasionally encounter patients who require unexpected long-term device support, depending on blood type, body size, and allosensitization. Consequently, long-term CF-LVAD therapy has become a more important option for the treatment of end-stage heart failure. Furthermore, with the current 1-year survival of this therapy being almost equivalent to that of cardiac transplantation, the topic on whether mechanical circulatory support could play a role of replacement for heart transplantation in patients with stage D heart failure is being actively discussed.⁶⁻⁸ However, compared with transplantation, more clinical data from long-term follow-up studies are necessary to evaluate the risks and benefits of CF-LVADs. In this study, we reviewed our single-center experience with CF-LVADs through a long-term follow-up study.

METHODS

The institutional review board of the Columbia University Medical Center approved this study. We retrospectively reviewed our experience with the CF-LVAD at the Columbia Presbyterian Medical Center between March 2004 and June 2010. During this period, 140 consecutive patients with end-stage heart failure who underwent the insertion of a CF-LVAD were included in this study. Preoperative variables that may correlate with survival were retrospectively collected for each patient. Most of these variables were selected on the basis of previous LVAD risk scores.⁹ The cohort consisted of 111 men with a mean age of 55 years. The initial

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Abbreviations and Acronyms

AI	= aortic insufficiency
BTT	= bridge to transplantation
CF-LVAD	= continuous-flow left ventricular assist device
DT	= destination therapy
GI	= gastrointestinal
INTERMACS	= Interagency Registry for Mechanically Assisted Circulatory Support
LVAD	= left ventricular assist device
RVAD	= right ventricular assist device
TR	= tricuspid regurgitation

strategy for LVAD insertion was BTT in 115 patients (82%) and DT in 25 patients (18%). The baseline patient characteristics are shown in [Table 1](#).

Devices and Concomitant Surgery

LVAD support was provided by 117 HeartMate II devices (Thoratec Corp, Pleasanton, Calif), 9 VentrAssist devices (Ventracor Ltd, Chatswood, NSW, Australia), 8 DuraHeart devices (TerumoHeart, Ann Arbor, Mich), and 6 DeBakey devices (MicroMed Technology, Inc, Houston, Tex). Various concomitant procedures were performed during LVAD insertion ([Table 2](#)). Of note, 39 patients (28%) underwent tricuspid annuloplasty (suture annuloplasty in 2, ring annuloplasty in 37), and 13 patients (9.2%) underwent aortic valve repair. Two patients (1.4%) in whom severe right ventricular failure developed in the operating room required concomitant right ventricular assist device (RVAD) insertion with a CentriMag system (Thoratec Corp).

Postimplant Anticoagulation and Follow-up

After device implantation, a standardized anticoagulation therapy with aspirin and warfarin was implemented. In patients receiving the HeartMate II device, a target international normalized ratio (INR) range was 2 ± 0.5 . After discharge, patients' anticoagulation was managed by nurse-practitioners with repeat testing frequency dictated by ease or difficulty in maintaining the patient within target INR range. Anticoagulation therapy was held in the event of bleeding and resumed once bleeding stopped. Patients were followed up at 1 week after initial discharge and then monthly unless there was an issue. There was no shared-care center during this study period. The frequency of clinic visits varied among patients depending on medical issues and the distance from a patient's home.

Follow-up and Postoperative Data Collection

The follow-up examinations were completed in June 30, 2013, and extended from 0 to 8.5 years (median, 3.6 years; interquartile range, 2.1–4.8 years). Clinical follow-up was completed in 98% of patients. To evaluate the early and late outcomes of patients during on-device support, all clinical data were collected until the patient reached 1 of 3 end points (death, transplant, or device explant for recovery). Late adverse events requiring rehospitalization included major bleeding events, such as gastrointestinal (GI) tract bleeding and significant epistaxis; device-related events, such as pump malfunction, thrombi, and infection; major cerebral events; recurrent heart failure; cardiac arrhythmia; infections not related to LVAD; and other various reasons. For patients receiving BTT, follow-up data after the cardiac transplantation also were collected.

To assess the time course of end-organ function after LVAD insertion, biochemical data, including blood urea nitrogen, creatinine, total and direct

bilirubin, alanine aminotransferase, and aspartate aminotransferase levels, were collected at 1 and 6 months and at 1, 2, and 3 years after the LVAD insertion.

Echocardiographic reports were retrospectively reviewed to assess the time course of the left ventricular dimension, aortic insufficiency (AI) severity, and tricuspid regurgitation (TR) severity. AI and TR severities were graded as none to trace, mild, mild-to-moderate, moderate, moderate-to-severe, and severe. AI and TR were considered to be significant if the grades were mild-to-moderate or greater.¹⁰ The data before; at 1 and 6 months after; and at 1, 2, and 3 years after LVAD insertion also were collected.

Statistical Analysis

The data represent frequency distributions and percentages. Continuous variables are expressed as mean $\pm$ standard deviation and compared using 2-sample *t* tests. Categorical variables were compared using the chi-square test. Kaplan–Meier analysis was used to calculate survival along with a log-rank *P* value when comparing groups. Patients were censored for transplantation and native heart recovery to calculate estimated on-device survival. Patients were stratified by preoperative variables, including age, cause of heart failure, implant era (before or after approval of the HeartMate II device by the Food and Drug Administration), device type (HeartMate II or others), and the HeartMate II Risk Score profiles.¹¹ Logistic regression was used to identify correlates of overall mortality during LVAD support. Continuous variables were dichotomized using the median value. Because of the small number of patients reviewed and lack of sufficient power, multivariate analysis was not performed. For multiple group comparison, mixed maximum likelihood regression models with log-transformed values were used.

RESULTS**Early and Late Clinical Outcomes**

Early and late mortality and morbidity rates are listed in [Table 3](#). The in-hospital mortality rate was 7.9% (*n* = 11). Seven patients (5.0%) had major stroke events, 2 of whom died. During hospitalization, 5 patients required delayed RVAD insertion for refractory right ventricular failure at 1 to 60 days after LVAD insertion. Of the 7 patients who eventually required RVAD support, 4 died (3 of multiorgan failure, 1 of a hemorrhagic stroke) and 3 were successfully bridged to transplantation. There were 13 late deaths during LVAD support after discharge. The leading cause of late death was device-related issues (device thrombus requiring device exchange in 1 case, sudden device malfunction in 3 cases, and operator error in battery exchange at home in 1 case). Overall, 24 patients (17%) died on LVAD support during a mean duration of 1.2 years (range, 0.011–7.5 years). Kaplan–Meier analysis showed an estimated on-device survival at 1, 3, and 5 years of 83%, 75%, and 61%, respectively ([Figure 1, A](#)). There were no statistically significant differences in in-hospital mortality and 1-year on-device survival among patients when stratified by preoperative variables including age, cause of heart failure, implant era, device type, and the HeartMate II risk score ([Table 4](#)).

[Table 5](#) demonstrates the risk factor analysis of overall mortality during LVAD support. Preoperative use of

TABLE 1. Baseline characteristics

Variables	N = 140
Age, y, mean $\pm$ SD	54.7 $\pm$ 14.4 y
Age groups, n (%)	
≤ 45 y	38 (27.1)
>45 - ≤ 60 y	45 (32.1)
>60 - ≤ 80 y	57 (40.7)
Gender, male, n (%)	111 (79.3)
Hypertension, n (%)	60 (42.9)
Diabetes mellitus, n (%)	44 (31.4)
Hyperlipidemia, n (%)	35 (25.0)
Cause of heart failure, n (%)	
Idiopathic cardiomyopathy	80 (57.1)
Ischemic cardiomyopathy	51 (36.4)
Others	9 (6.4)
Intention to treat, n (%)	
BTT	115 (82.1)
DT	25 (17.9)
Inotropes support, n (%)	116 (82.9)
Ventilator support, n (%)	2 (1.4)
IABP support, n (%)	35 (25.0)
Mechanical circulatory support, n (%)	15 (11)
ICD, n (%)	116 (82.9)
Reoperation, n (%)	37 (26.4)
BMI, mean $\pm$ SD	26.1 $\pm$ 5.2
Obese, n (%)	28 (20.0)
BSA in m ² , mean $\pm$ SD	1.93 $\pm$ 0.2
BSA >2 , n (%)	56 (40.0)
Ejection fraction (%)	15.9 $\pm$ 6.4
Systolic blood pressure (mm Hg)	101.9 $\pm$ 17.6
Mean PAP (mm Hg)	35.4 $\pm$ 9.6
PCWP (mm Hg)	24.7 $\pm$ 8.5
CVP (mm Hg)	11.6 $\pm$ 6.4
CO (L/min)	3.0 $\pm$ 0.95
PVR (Wood units)	4.1 $\pm$ 2.7
Sodium (mmol/L)	133 $\pm$ 4.5
BUN (mg/dL)	34 $\pm$ 17
Creatinine (mg/dL)	1.5 $\pm$ 0.64
Total protein (g/dL)	6.7 $\pm$ 0.85
Albumin (g/dL)	3.6 $\pm$ 0.55
ALT (IU/L)	41 $\pm$ 64
AST (IU/L)	67 $\pm$ 199
Total bilirubin (mg/dL)	1.5 $\pm$ 0.90
Direct bilirubin (mg/dL)	0.48 $\pm$ 0.38
WBC ($\times 1000$ /mL)	8.8 $\pm$ 3.5
Hemoglobin (g/dL)	11 $\pm$ 2.0
HCT (%)	34 $\pm$ 5.7
Platelets ($\times 1000$ /mL)	216 $\pm$ 70
INR	1.3 $\pm$ 0.37

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; BTT, bridge to transplantation; BUN, blood urea nitrogen; CO, cardiac output; CVP, central venous pressure; DT, destination therapy; HCT, hematocrit; IABP, intra-aortic balloon pump; ICD, implantable cardioverter-defibrillator; INR, international normalized ratio; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SD, standard deviation; WBC, white blood cells.

intra-aortic balloon pump, baseline hemoglobin, hematocrit, and albumin level were significant predictors of mortality.

TABLE 2. Concomitant surgical procedures

Tricuspid valve repair, n (%)	39 (28)
Aortic valve repair, n (%)	13 (9.3)
Aortic valve replacement, n (%)	1 (0.71)
Closure of prosthetic aortic valve, n (%)	2 (1.4)
Mitral valve repair, n (%)	3 (2.1)
PFO closure, n (%)	9 (6.4)
Left ventricular aneurysmectomy, n (%)	2 (1.4)
Concomitant RVAD insertion, n (%)	2 (1.4)

PFO, Patent foramen ovale; RVAD, right ventricular assist device.

A total of 84 patients (60%) underwent 169 rehospitalizations (209 patient-years) related to adverse events (Table 3). The leading causes of readmission included major bleeding events, recurrent heart failure, device thrombus/malfunction, device infection, and cardiac arrhythmia. The adverse event rates (number of events/patient-year) are listed in Table 3. The freedom from rehospitalization rates for hospital survivors at 1 and 3 years were 31% and 6.9%, respectively (Figure 1, B).

TABLE 3. Early and late mortality and morbidity during continuous-flow left ventricular assist device support

In-hospital mortality, n (%)	11 (7.9)
Multiorgan failure	5 (3.6)
Stroke	2 (1.4)
Miscellaneous cause	2 (1.4)
Sepsis	1 (0.71)
Heparin-induced thrombocytopenia	1 (0.71)
In-hospital morbidity, n (%)	
Cardiac arrhythmia	33 (24)
Reoperation for bleeding	22 (16)
Acute renal failure requiring dialysis	16 (11)
Sepsis	7 (5.0)
Stroke	7 (5.0)
RVAD use	7 (5.0)
Venovenous ECMO use	1 (0.71)
Late mortality, n (%)	13 (9.3)
Device-related	5 (3.6)
Stroke	1 (0.71)
Respiratory failure	1 (0.71)
Sepsis	1 (0.71)
Miscellaneous cause	5 (3.6)
Rehospitalization, no. of events (per patient-y)	
Bleeding	30 (0.14)
Device thrombus/malfunction	19 (0.091)
Device infection	21 (0.10)
Heart failure	26 (0.12)
Cardiac arrhythmia	16 (0.077)
Stroke	9 (0.043)
LVAD nonrelated infection	11 (0.053)
Device alarm without mechanical abnormality	12 (0.057)
TIA or syncope	8 (0.038)
Psychiatric issues	3 (0.014)
Others	14 (0.067)

ECMO, Extracorporeal membrane oxygenation; LVAD, left ventricular assist device; RVAD, right ventricular assist device; TIA, transient ischemic attack.

FIGURE 1. A, On-device survival of the entire cohort. B, Freedom from rehospitalization rate for any reason.

A total of 14 patients (10%) (13 HeartMate II pumps and 1 DeBakey pump) underwent pump replacement because of device thrombosis ($n = 5$), driveline fracture ($n = 3$), infection ($n = 2$), and other reasons ($n = 4$). The median time to pump replacement was 1.6 years (range, 0.019-4.9 years). Pump replacement was performed through a median full sternotomy ($n = 9$) or subcostal incision ($n = 5$).¹² There were 2 in-hospital deaths in the full-sternotomy group. The rates of freedom from pump replacement at 1, 2, 3, and 5 years were 94%, 83%, 69%, and 51%, respectively.

Patients on Device Support More Than 3 Years

A total of 24 patients (17%) had been on LVAD support for more than 3 years (mean, 3.9 years; range, 3.0-7.5 years). The devices used included the HeartMate II in 23 patients and the VentrAssist in 1 patient. Three patients were bridged to transplantation, and 5 patients were listed for transplantation. There were 63 major adverse events in 22 patients (92%). Eighteen patients (75%) underwent

multiple readmissions. The annual rehospitalization rate was 2.3 per patient-year for the first year (17 events in 12 patients), 1.8 per patient-year for the second year (17 events in 14 patients), 2.3 per patient-year for the third year (18 events in 11 patients), and 1.5 per patient-year during the 3-year follow-up period (11 events in 8 patients).

Bridge to Transplantation, Recovery, and Destination Therapy

A total of 94 patients (67%) were successfully bridged to transplantation after a mean of 0.76 years of LVAD support (range, 0.074-3.9 years). The initial strategies were BTT in 92 patients and DT in 2 patients. The BTT rate in patients who were initially eligible for transplantation was 79%. The in-hospital mortality rate after transplantation in these BTT cases was 5.3% ($n = 5$). The actuarial survivals after transplantation at 1, 3, and 5 years were 88%, 86%, and 80%, respectively. One patient with doxorubicin-induced cardiomyopathy was successfully bridged to recovery after

TABLE 4. In-hospital mortality and on-device survival at 1 year stratified by preoperative variables

Variable	No. of patients (%)	In-hospital mortality (%)	P value	Survival at 1 y (%)	P value
Age					
≤45 y	38 (27.1)	7.89		86.0	
>45-≤60 y	45 (32.1)	8.89		79.6	
>60-≤80 y	57 (40.7)	7.02	.94	83.8	.91
Cause					
Idiopathic cardiomyopathy	80 (57.1)	7.50		82.3	
Ischemic cardiomyopathy	51 (36.4)	7.84	.94	81.2	.59
Implant era					
March 2004 to April 2008	47 (33.6)	10.6		71.1	
May 2008 to June 2010	93 (66.4)	6.45	.33	86.9	.19
Device type					
HeartMate II (Thoratec Corp, Pleasanton, Calif)	117 (83.6)	6.84		83.3	
Others	23 (16.4)	13.0	.31	77.9	.86
HMRS†					
Low risk (≤1.58)	76 (54.3)	5.26		87.8	
Medium risk (1.58-2.48)	48 (34.3)	8.33		77.4	
High risk (>2.48)	16 (11.4)	18.8	.19	72.2	.22

HMRS, HeartMate II Risk Score. *Enter value of 1 if total center LVAD volume is <15 and 0 if ≥15.¹¹ †HMRS = $(0.0274 \times [\text{age in years}]) \times (0.723 \times [\text{albumin g/dL}]) \times (0.74 \times [\text{creatinine mg/dL}]) \times (1.136 \times [\text{international normalized ratio}]) \times (0.807 \times [\text{center LVAD volume} <15^*])$.

0.91 years of LVAD support. However, this patient experienced recurrent stage D heart failure 6 months after device removal, required LVAD reinsertion, and was eventually bridged to transplantation. The patients receiving DT received LVAD support for an average of 3.2 years (range, 0.010-7.5 years). Nine patients receiving DT died during the support period. The on-device survival was similar between the BTT and DT groups ($P = .79$).

End-Organ Function During Continuous-Flow Left Ventricular Assist Device Support

Table 6 demonstrates the time course of hepatic and renal function before and after CF-LVAD insertion. End-organ function was restored 1 month after initiation of support. These improvements had been sustained throughout the support period except for creatinine level. Three-year longitudinal data were available in 19 patients. Mean creatinine level in this group was 1.5 ± 0.50 at baseline, which decreased to 1.1 ± 0.39 at 1 month ($P = .050$, vs baseline) and increased to 1.4 ± 0.48 at 3 years ($P = .61$, vs baseline).

Change of Left Ventricular Dimension, Aortic Insufficiency, and Tricuspid Regurgitation

Figure 2 shows the serial change of left ventricular diastolic dimension during LVAD support. Left ventricular diastolic dimension significantly decreased from 69 ± 11 mm to 58 ± 11 mm at 1 month after LVAD support ($P < .0001$); thereafter, the dimension has remained stable.

The ratio of significant AI increased over time (Figure 3, A). One third of patients had more than mild-to-moderate AI in the late period. In 13 patients who underwent concomitant aortic valve repair, 1 had recurrent severe

AI at 1 month after initial surgery. Others had less than mild AI during a mean follow-up of 1.4 years (range, 0.11-3.5 years).

Of the 15 patients who required readmission because of heart failure, 6 had typical right-sided heart failure symptoms (eg, leg edema) and 8 had typical left-sided symptoms (eg, shortness of breath). Biventricular failure symptoms developed in 1 patient. Seven of 17 patients (41%) with significant AI at any postoperative point underwent rehospitalization because of left-sided heart failure compared with 2 of 113 patients (1.8%) who did not have significant AI ($P < .0001$). The ratio of significant TR decreased from 45% to 22% at 1 month after LVAD insertion and remained at approximately 20% during follow-up (Figure 3, B). In those undergoing concomitant tricuspid surgery ($n = 39$), 3 patients had recurrent TR (mild-to-moderate in 2, severe in 1) during follow-up. TR severity was consistently less than mild in all the other patients. Similar to those with AI, 5 of 33 patients (15%) with significant TR at any postoperative point were rehospitalized because of right-sided heart failure compared with 2 of 97 patients (2.0%) who did not have significant TR ($P = .012$).

DISCUSSION

This study demonstrated our single-center experience of CF-LVADs as a long-term therapy for patients with heart failure. Satisfactory long-term on-device survivals of 83% at 1 year, 75% at 3 years, and 61% at 5 years were obtained. Because the prospective, randomized clinical trial demonstrated a significant improvement in survival and device durability with the CF-LVAD compared with the pulsatile-flow LVAD, use of the CF pump has rapidly

TABLE 5. Predictors of on-device mortality, N = 140

Variables	On-device mortality, n (%)		OR, 95% CI	P value
	Yes (24)	No (116)		
Age groups (Ref: ≤ 45 y)				.93
>45- ≤ 60 y	8 (33.3)	37 (31.9)	1.02 (0.35-2.93)	
>60- ≤ 80 y	10 (41.7)	47 (40.5)	0.86 (0.31-2.41)	
Gender (Ref: female)				
Male	19 (79.2)	92 (79.3)	1.24 (0.46-3.35)	.67
Obesity (BMI >30 kg/m ²) (Ref: No)	7 (29.2)	21 (18.1)	1.55 (0.64-3.73)	.33
Hypertension (Ref: No)	10 (41.7)	50 (43.1)	0.79 (0.35-1.79)	.57
Diabetes (Ref: No)	7 (29.2)	37 (31.9)	0.74 (0.31-1.79)	.50
Hyperlipidemia (Ref: No)	4 (16.7)	31 (26.7)	0.58 (0.20-1.71)	.32
Cause of heart failure (Ref: idiopathic cardiomyopathy)				.85
Ischemic cardiomyopathy	8 (33.3)	43 (37.1)	0.78 (0.33-1.88)	
Others	2 (8.3)	7 (6.0)	1.06 (0.24-4.71)	
DT (Ref: BTT)	9 (37.5)	16 (13.8)	1.57 (0.65-3.81)	.32
Inotropes support (Ref: No)	16 (66.7)	100 (86.2)	0.47 (0.20-1.11)	.087
IABP support (Ref: No)	9 (37.5)	26 (22.4)	2.77 (1.18-6.48)	.019
ICD (Ref: No)	19 (79.2)	97 (83.6)	0.78 (0.29-2.09)	.62
Reoperation (Ref: No)	9 (37.5)	28 (24.1)	1.26 (0.54-2.91)	.59
Ejection fraction ≥ 15 (%)	14 (58.3)	69 (59.5)	1.04 (0.48-2.42)	.86
Systolic blood pressure ≥ 101 (mm Hg)	8 (33.3)	49 (42.2)	0.68 (0.29-1.59)	.37
CVP ≥ 11 (mm Hg)	5 (20.8)	26 (22.4)	0.96 (0.36-2.58)	.94
PAP ≥ 36 (mm Hg)	9 (37.5)	53 (45.7)	0.75 (0.33-1.72)	.50
PCWP ≥ 25 (mm Hg)	10 (41.7)	55 (47.4)	0.84 (0.37-1.89)	.67
CO ≥ 3.0 (L/min)	14 (58.3)	48 (41.4)	1.59 (0.70-3.59)	.26
PVR ≥ 3.5 (Wood units)	9 (37.5)	52 (44.8)	0.80 (0.35-1.83)	.59
WBC ≥ 8.2 ($\times 1000$ /mL)	14 (58.3)	57 (49.1)	1.64 (0.72-3.71)	.23
Hemoglobin ≥ 11 (g/dL)	8 (33.3)	63 (54.3)	0.38 (0.16-0.90)	.028
HCT ≥ 34 (%)	8 (33.3)	62 (53.5)	0.38 (0.15-0.91)	.030
Platelets ≥ 211 ($\times 1000$ /mL)	11 (45.8)	58 (50.0)	1.02 (0.45-2.30)	.96
Sodium ≥ 134 (mmol/L)	11 (45.8)	63 (54.3)	0.68 (0.31-1.53)	.36
BUN ≥ 31.5 (mg/dL)	14 (58.3)	55 (47.4)	1.38 (0.60-3.11)	.44
Creatinine ≥ 1.5 (mg/dL)	16 (66.7)	54 (46.6)	2.05 (0.88-4.80)	.098
Total protein ≥ 6.7 (g/dL)	12 (50.0)	60 (51.7)	0.85 (0.38-1.89)	.68
Albumin ≥ 3.6 (g/dL)	9 (37.5)	71 (61.2)	0.37 (0.16-0.85)	.019
Total bilirubin ≥ 1.15 (mg/dL)	13 (54.2)	56 (48.3)	1.45 (0.65-3.26)	.37
Direct bilirubin ≥ 0.35 (mg/dL)	14 (58.3)	54 (46.6)	1.80 (0.79-4.07)	.16
AST ≥ 25 (IU/L)	11 (45.8)	60 (51.7)	0.75 (0.34-1.67)	.48
ALT ≥ 23 (IU/L)	10 (41.7)	62 (53.5)	0.70 (0.31-1.58)	.39
INR ≥ 1.2	12 (50.0)	54 (46.6)	1.29 (0.58-2.89)	.53

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BTT, bridge to transplantation; BUN, blood urea nitrogen; CI, confidence interval; CO, cardiac output; CVP, central venous pressure; DT, destination therapy; HCT, hematocrit; IABP, intra-aortic balloon pump; ICD, implantable cardioverter-defibrillator; INR, international normalized ratio; OR, odds ratio; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; Ref, reference; WBC, white blood cells.

increased.¹⁻⁴ After the increase in clinical experience with these devices, improvements in outcomes have been reported. The original HeartMate II BTT trial including patients post-transplant demonstrated a 1-year overall survival of 68%,¹ which has improved to 85% according to more recent data.³ Even more recently, the ADVANCE Bridge to Transplant Trial with another CF pump (HeartWare ventricular assist device, HeartWare Inc, Framingham, Mass) showed 94% on-device survival at 180 days after implantation or explantation to receive a cardiac transplantation or for recovery.¹³

In the HeartMate II DT trial, 2-year survival improved from 58% in the early era to 63% in the later era.¹⁴ Thus, in the current era, excellent early and midterm survivals can be expected with CF pump technology. However, longer-term data over 2 years remain limited. The current data shed light on the paucity of long-term data for CF-LVAD therapy.

From the current results, better long-term survival can be largely expected from postdischarge patient treatment because most patients on long-term device support underwent rehospitalization. The leading causes of readmission

TABLE 6. Time course of hepatic and renal function during continuous-flow left ventricular assist device support

	Baseline n = 141	1 mo n = 130	6 mo n = 77	1 y n = 51	2 y n = 28	3 y n = 19	P value
AST (IU/L)	41 ± 64	27 ± 13	34 ± 15	35 ± 17	27 ± 10	27 ± 9.1	.81
ALT (IU/L)	67 ± 199	22 ± 15	31 ± 17	31 ± 26	21 ± 8.9	20 ± 11	.014
Total bilirubin (mg/dL)	1.5 ± 0.90	0.96 ± 0.65	0.91 ± 0.48	0.85 ± 0.48	0.83 ± 0.33	0.71 ± 0.27	<.0001
BUN (mg/dL)	34 ± 17	22 ± 11	27 ± 12	27 ± 12	23 ± 9.6	24 ± 11	.012
Creatinine (mg/dL)	1.5 ± 0.62	1.1 ± 0.45	1.3 ± 0.48	1.4 ± 0.47	1.3 ± 0.36	1.4 ± 0.48	.17

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen.

were bleeding, cardiac-related causes (heart failure or arrhythmia), and device-related morbidities. These issues in the chronic phase are somewhat unique compared with those in the acute phase such as stroke, sepsis, and organ failure. Hashin and colleagues¹⁵ recently reported similar findings. They reported a readmission rate of 1.64 per patient-year with a mean follow-up of 1.4 years. Of note, the readmission rate decreased from 2.0 per patient-year to 1.2 per patient-year during the first 6 months and then stabilized. In our specific population of patients who had been on device support for a mean of 4 years, there was a peak in the rehospitalization rate in the first year and another peak in the third year (2.3 per patient-year for both years). These differences may result from our longer follow-up period. In the third year, 5 of 18 events resulted from device-related issues, including 3 pump replacements.

GI tract bleeding and epistaxis have emerged as a major source of morbidity in patients with CF-LVADs.¹⁶ Possible mechanisms with obligate device anticoagulation include acquired von Willebrand disease,¹⁷ GI tract arteriovenous malformations associated with reduced pulsatility,¹⁸ and impaired platelet aggregation.¹⁹ The management of bleeding issues is inextricably linked to the risk of thromboembolic events. However, considering the individual risks and benefits, careful adjustment of anticoagulation and antiplatelet therapy seems to be the only method for treating

this complication. Further understanding of the mechanisms underlying bleeding and novel strategies such as new anticoagulant drugs will play an important role in the long-term management of CF-LVAD therapy.

The development of de novo AI during CF-LVAD support has been reported.^{10,20} Consistent with those reports, the current study demonstrated worsening of AI over time. At 2 to 3 years of follow-up, approximately 30% of patients had significant AI. Significant AI can cause the recycling of blood flow from the LVAD outflow graft into the left ventricle and result in decreased forward cardiac output, inadequate ventricular unloading, and increased pump work. Toda and colleagues²¹ reported that de novo AI had

FIGURE 2. Serial change of left ventricular diastolic dimension during CF-LVAD support. LVEDD, Left ventricular end-diastolic diameter.

FIGURE 3. Time course of significant (A) AI and (B) TR rate during CF-LVAD support. AI, Aortic insufficiency; TR, tricuspid regurgitation.

a significant negative impact on survival during long-term pulsatile LVAD support. In our study, patients with extensive AI during long-term CF-LVAD support were at significant risk of recurrent left-sided heart failure. In our current practice, to prevent the future development of AI, we aggressively perform the concomitant aortic valve procedure for cases with more than mild-to-moderate AI.²² Although recurrence developed in 1 patient who had preoperative severe AI, the outcome of concomitant aortic valve plasty seems satisfactory. With regard to TR, approximately 20% of patients constantly had a significant degree of regurgitation. The presence of significant TR usually reflects right ventricular dysfunction or volume overload status. In our study, as noted with AI, TR also had a significant negative impact on late functional status. Piacentino and colleagues²³ demonstrated that the use of a concomitant tricuspid valve procedure can efficiently eliminate TR and prevent postoperative right ventricular heart failure. Therefore, concomitant aortic and tricuspid valve plasty or replacement depending on valve pathology should be considered for patients who need long-term CF-LVAD support.

Cardiac arrhythmia, especially ventricular arrhythmia, also was a common issue in the early and late periods. Although such arrhythmia may not be lethal in the presence of LVAD, it could put patients at risk of right ventricular failure. In addition to implantable cardioverter-defibrillator therapy, interventions aimed at minimizing the risk of recurrent arrhythmias, such as antiarrhythmic medication use, catheter ablation, and even intraoperative cryoablation, may be considered.^{24,25}

In our study, device-related events were the leading cause of late death and morbidity. Fourteen patients (10%) required device exchange at a median time of 1.6 years. Most recently, Moazami and colleagues²⁶ reported pump exchange data from multicenter clinical trials. A total of 72 (6.4%) of 1128 patients with a HeartMate II device required an exchange at a median time of 428 days after the initial implantation. The freedom from device replacement rate at 2 years was 87% before 2007 and 92% since 2007. In our study, the freedom from device exchange rate was 94% at 1 year, 83% at 2 years, 69% at 3 years, and 51% at 5 years. Although advances in technology certainly improve device durability, prolonged device use will inevitably result in mechanical issues. Our novel echocardiography ramp test is helpful to detect device malfunction in patients with CF-LVADs.²⁷ Routine monitoring may reduce the incidence of late mortality and morbidity associated with sudden device malfunction. In regard to the surgical approach to device exchange, the subcostal approach is currently our preferred method because it is less invasive and has better outcomes.^{12,28}

Another interesting aspect of this study is the long-term effect of continuous blood flow on renal and hepatic

function. Studies have demonstrated no deleterious effects of reduced pulsatility on end-organ function in the 6- to 15-month time period.^{29,30} Our findings confirm that the use of CF-LVADs can improve renal and hepatic function with longer-term follow-up. Only the creatinine level returned to the baseline value at 3 years. This trend might be explained by the repeated rehospitalizations requiring renally toxic medications, such as antibiotics and overdoses of diuretics. In our cohort, 1 patient receiving DT in whom renal failure developed required dialysis after prolonged antibiotic therapy for bacteremia. A further detailed study would be desirable to evaluate the long-term effect of CF-LVAD therapy on renal function.

Active discussion continues about the long-term use of CF-LVADs as an alternative to cardiac transplantation. The current post-transplant survivals at 1, 2, 5, and 10 years are approximately 90%, 80%, 70%, and 50%, respectively.³¹ Kirklin and colleagues⁶ recently summarized a large body of data from the INTERMACS Registry including 1160 patients receiving DT. After excluding patients requiring biventricular support and notable preoperative risk factors such as cardiogenic shock, patients receiving DT within this cohort had 1- and 2-year survivals of 88% and 80%, respectively, with CF-LVADs.⁶ Our on-device survival data also support the utility of CF-LVADs. Excellent post-transplant survival in patients receiving BTT can reduce the need for cardiac transplantation as a first-line replacement therapy. However, it is too premature to make conclusions about survival comparisons because of the lack of head-to-head comparative data. Furthermore, considering the frequent readmissions in this population, patient survival, quality of life, and health care costs should be taken into account before conclusions are drawn.⁷

Study Limitations

First, the study was a retrospective analysis of a single-center experience. Although recent multicenter studies have shown evidence of the excellent CF-LVAD outcomes, the strength of the present single-center study was the large number of patients receiving CF-LVADs with consistent strategies in patient selection, operative procedure, and postoperative management. Furthermore, the present study included detailed analyses of serial echocardiography, end-organ function, and clinical follow-up outcomes that could not be addressed in the multicenter studies. Second, the number of patients receiving DT who were deemed to be candidates for long-term support was low. For patients receiving BTT, a rather short support time was expected as an initial intent. However, the constant shortage of available donors has resulted in an increasing number of patients receiving BTT with longer waiting times on CF-LVAD support. In the present cohort, 30 of 115 patients receiving BTT (26%) required CF-LVAD support for more than 1 year. Furthermore, INTERMACS registry data demonstrate that

patients often have long durations of support regardless of initial implant strategy, and strategies often change over time.³² Thus, in the current continuous-flow era, device intent of BTT and DT becomes less representative of the clinical circumstances. Third, the number of readmissions to other hospitals was not recorded; thus, the overall incidence may be underestimated. Finally, various devices were included in this study. However, we intended to reflect the actual conditions prevailing in CF-LVAD therapy because various technologies emerge rapidly.

CONCLUSIONS

Current CF-LVADs provide satisfactory long-term survival, although rehospitalization for specific reasons in this population was common. With appropriate device and patient management, acceptable survivals at more than 3 years can be expected in select patients.

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