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Incidence and clinical significance of late right heart failure during continuous-flow left ventricular assist device support

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KEYWORDS:
continuous flow;
right heart failure;
transplantation;
ventricular assist device;
Bridge to transplant;
Destination therapy

BACKGROUND: Right heart failure (RHF) is an unresolved issue during continuous-flow left ventricular assist device (LVAD) support. Little is known about the incidence and clinical significance of late RHF during LVAD support.

METHODS: Between May 2004 and December 2013, 336 patients underwent continuous-flow LVAD implantation. Of these, 293 patients (87%) discharged with isolated LVAD support were included in this study. Late RHF was defined as HF requiring re-admission and medical or surgical intervention after initial surgery.

RESULTS: Late RHF occurred in 33 patients (11%) at a median of 99 days after discharge (range 19 to 1,357 days). Freedom from late RHF rates were 87%, 84% and 79% at 1, 2 and 3 years, respectively. RHF recurred in 15 patients. Three patients required right ventricular assist device insertion. Univariable Cox proportional hazards regression model showed diabetes mellitus (HR 2.05, 95% CI 1.03 to 4.06, $p = 0.04$), body mass index >29 (HR 2.47, 95% CI 1.24 to 4.94, $p = 0.01$) and blood urea nitrogen level >41 mg/dl (HR 2.19; 95% CI 1.10 to 4.36; $p = 0.025$) as significant predictors for late RHF. Estimated on-device survival rates at 2 years were 73% in the RHF group and 82% in the non-RHF group ($p = 0.20$). However, overall survival at 2 years was significantly worse in patients who developed late RHF (60% vs 85%, $p = 0.016$). This reduction was mostly attributed to worse overall outcomes in the bridge-to-transplant (BTT) population.

CONCLUSIONS: Late RHF is common after continuous-flow LVAD implantation, but does not affect survival during LVAD support. However, it is associated with worse overall outcomes in the BTT population.

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Continuous-flow left ventricular assist device (LVAD) use has become standard care among patients with advanced heart failure.[1,2] Clinical outcomes continue to improve through better patient selection, surgical techniques and peri-operative management.[3,4] The data from the Inter-agency Registry for Mechanically Assisted Circulatory Support (INTERMACS) show that current 1- and 2-year survival rates reached 80% and 70%, respectively.[5] These favorable mid-term results have encouraged the increased use of continuous-flow LVADs.

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Despite these improvements, right heart failure (RHF) after LVAD implantation remains an unresolved issue. Approximately 20% of patients develop some form of RHF after contemporary continuous-flow LVAD placement.[6] Numerous studies have shown that RHF after LVAD insertion is a serious complication associated with poor outcomes and have identified risk factors for RHF development.[5–8] However, most published data focused on RHF occurring during the early phase after LVAD implantation.

In contrast to the continued improvement in survival with use of continuous-flow LVADs, there is an emerging issue about late adverse events and re-admissions during long-term LVAD support.[9,10] Despite decreasing rates of adverse events compared with pulsatile-flow LVADs,[1,2] re-admission because of device-related or unrelated complications is still frequently required. Although cardiac pathologies, including heart failure and arrhythmia, are leading causes of re-admission,[9,10] less certainty exists with regard to how many patients will develop clinically significant RHF late after LVAD implantation and how the RHF will impact outcomes. Thus, the aim of this study was to assess the incidence and clinical significance of late RHF during continuous-flow LVAD support.

Methods

Our institutional review board approved this study. We retrospectively reviewed our experiences with continuous-flow LVADs at the Columbia Presbyterian Medical Center between April 2004 and December 2013. During this period, 336 consecutive patients with advanced heart failure underwent continuous-flow LVAD insertion as either a bridge to transplant (BTT) or as destination therapy (DT). Patients who required long-term mechanical support with contraindications to heart transplantation, including elderly patients and those with non-reversible comorbidities, were placed on an LVAD as DT. Of these, 293 patients (87%) who were discharged with isolated LVAD support were included in this study.

Device used and concomitant valve procedures

Devices used as LVAD support included 252 HeartMate II (Thoratec Corp., Pleasanton, CA), 6 VentrAssist LVADs (Ventracor, Ltd., Chatswood, NSW, Australia), 7 DuraHeart LVASs (TerumoHeart, Ann Arbor, MI), 4 DeBakey VADs (MicroMed Technology, Inc., Houston, TX) and 24 HeartWare HVADs (HeartWare International, Inc., Framingham, MA).

In patients with mild or greater aortic insufficiency, either aortic valve repair or replacement with a tissue valve was performed. In most cases, aortic valve was repaired by approximating the raphe of each leaflet. Patients with a mechanical valve in the aortic position underwent the aortic valve oversewn with a patch. Mitral valve repair was performed in patients with severe functional mitral regurgitation according to discretion of the surgeon. The tricuspid valve was repaired in patients with moderate or greater tricuspid regurgitation. In cases with severe leaflet restriction or leaflet destruction by pacemaker leads, tricuspid valve replacement with a tissue valve was chosen.

Post-implant device management

After device implantation, all patients received a standardized heart failure medical regimen that included neurohormonal antagonists, diuretics and anti-arrhythmic agents, based on individual clinical pictures. Anti-coagulation therapy with aspirin and warfarin was implemented. The target international normalized ratio range varied according to device type. In HeartMate II patients, the target range was 2 ± 0.5. Before discharge, volume status was medically optimized in all patients. Furthermore, echocardiography was performed at our institution routinely for pump-speed optimization to ensure middle interventricular septum position and intermittent aortic valve opening while maintaining no more than mild mitral regurgitation.[11]

After discharge, nurse practitioners managed anti-coagulation with the repeat testing frequency dictated by the ease or difficulty of maintaining the patient within their target range. Anti-coagulation therapy was withheld in the event of bleeding and resumed once bleeding had stopped. Patients received follow-up at 1 week after the initial discharge and monthly thereafter unless an issue necessitated more frequent visits. Clinic visit frequency varied among patients depending on individual medical issues and travel distances.

Definition and management of late RHF

Late RHF was defined as right heart failure requiring rehospitalization after indexed hospital discharge and medical or surgical treatments, including strengthening of diuretics, inotropic support and right ventricular assist device (RVAD) implantation. Detection of RHF was based on clinical findings. Typical signs and symptoms of RHF included edema, weight gain, ascites and jugular venous distention. Clinical examination was performed on all of the patients by heart failure cardiologists. In this study, heart failure related to device failure or suspected device failure, such as device thrombosis, inflow and outflow obstruction or drive-line fracture, was not considered as late RHF. Each event was captured and assessed retrospectively by at least 2 reviewers (K.T. and S.H.). Patients were enrolled in the late RHF group if both reviewers agreed. Disagreements in "late RHF" interpretation were resolved by consensus.

Patients who were hospitalized due to symptoms of heart failure routinely underwent: (1) interrogation of the device and hemolysis work-up to rule out device failure and thrombosis; (2) implantable cardioverter-defibrillator/pacemaker interrogation to identify presence of arrhythmia that may have exacerbated RHF; and (3) echocardiography for optimization of pump speed. Initial medical management included intensification of diuretic therapy. Patients with severe RHF, as defined by the presence of end-organ dysfunction, underwent right heart catheterization, with inotropic therapy initiated if needed. In patients with medically refractory RHF, RVAD implantation was then considered.

Data collection and follow-up

All clinical data were collected through a review of electronic medical records. For each patient, pre-operative variables that could correlate with survival were retrospectively collected. These included baseline demographics, medical history, laboratory values and echocardiographic and hemodynamic parameters.

Intra-operative variables included concomitant procedures at the time of LVAD implantation, cardiopulmonary bypass time, aortic cross-clamp time, blood product use and nitric oxide use at

the time of implantation. Early post-implant data included complications occurring between the operation and hospital discharge. Major adverse events other than late RHF that required re-admission during LVAD support were also recorded. These included major bleeding events such as gastrointestinal tract bleeding and significant epistaxis; device-related events, such as pump thrombi and drive-line injury; major cerebral events; cardiac arrhythmia; and infections related or not related to LVAD. For BTT patients, follow-up clinical data after cardiac transplantation were also collected.

The follow-up examinations were completed on August 31, 2014, and the follow-up period in entire cohort lasted from 5 to 3,091 days (median 739 days, interquartile range 353 to 1,279 days) after index hospital discharge. Clinical follow-up was completed in 97% of the patients.

Statistical analysis

SPSS software (version 22.0, SPSS, Inc., Chicago, IL) was used for statistical analysis. The data are presented in frequency and percent for categorical variables and as mean ± standard deviation for continuous variables. Categorical variables were compared using Fisher's exact test, whereas continuous variables were compared using 2-sample *t*-tests. Kaplan–Meier curves were used to represent survival and were compared using the log-rank test. Patients were censored for transplantation and LVAD explant after recovery of the native heart to calculate estimated on-device survival. For overall survival analysis, all patients were censored on the date of death or at conclusion of the study. Cox proportional hazard regression was used to derive hazard ratios (HRs) and 95% confidence intervals (CIs) after testing for proportional hazard assumption using Schoenfeld residuals. Univariable analysis was performed to assess late RHF predictors on all baseline variables. Because of the small number of patients reviewed and lack of sufficient power, multivariate analysis was not performed. Continuous parameters were dichotomized at the 25th, 50th and 75th percentiles, and the percentile value with the lowest *p*-value was chosen. Dichotomization took place at the 75th percentile for blood urea nitrogen and body mass index (BMI). $p < 0.05$ was considered statistically significant for all analyses.

Results

Incidence of late RHF

Thirty-three patients (11%) developed RHF and required re-admission at a median of 141 days after LVAD implantation (range 45 to 1,379 days) and at a median of 99 days after indexed discharge (range 19 to 1,357 days). Three patients presented with ventricular tachyarrhythmia and 1 patient with systemic infection, which were likely factors predisposing to RHF. Fifteen patients required temporary inotropic support in addition to intensification of diuretic therapy. Right heart catheterization at the time of re-admission demonstrated elevating filling pressures in these patients: mean central venous pressure (CVP) 18 ± 4.9 mm Hg; mean pulmonary artery pressure 31 ± 8.2 mm Hg; and pulmonary capillary wedge pressure (PCWP) 20 ± 6.9 mm Hg. Three patients (1.0%) required RVAD at 59, 128 and 152 days after LVAD implantation. A CentriMag (Thoratec Corp.) was used for RVAD in all patients. Twenty-four patients (73%) developed RHF symptoms within 6 months after indexed hospital discharge. Rates for freedom from first re-admission related to RHF were 87%, 84% and 79% at 1, 2 and 3 years, respectively (Figure 1).

Baseline characteristics and peri-operative outcomes

Pre-operative patient characteristics at the time of LVAD implantation are shown in Table 1. Patients in the RHF group were more likely to have larger body surface area, higher BMI, diabetes mellitus, higher left ventricular ejection fraction and higher blood urea nitrogen and creatinine levels at the time of LVAD implantation compared with those in the non-RHF group (Table 1). The incidence of patients who had severely reduced right ventricular systolic function and significant tricuspid valve regurgitation was similar between the groups. Baseline hemodynamic parameters, including CVP and CVP/PCWP ratio, were also similar between the groups.

Table 2 summarizes intra- and early post-operative outcomes. No significant differences were found in device type used, cardiopulmonary bypass and aortic cross-clamp time, amount of blood product used and frequency of nitric oxide use. Patients in the RHF group more frequently underwent tricuspid valve replacement. During their hospital stay, patients in the RHF group were more likely to have renal failure requiring renal replacement therapy. In total, 7 patients in the BTT cohort required temporary RVAD support at 0 to 3 days after LVAD implantation. All were successfully weaned from the RVAD after 7 to 18 days of support. Of these, 1 patient had recurrence of late RHF. The incidence of early RHF requiring RVAD during indexed hospitalization was similar between the groups. The mean hospital stay in the entire cohort was 32 days and was similar between the groups. The mean pump speed at the time of indexed discharge in patients with a HeartMate II was 8,911 ± 386 rpm in the RHF group and 8,981 ± 423 rpm in the non-RHF group ($p = 0.42$).

Late adverse events other than RHF during LVAD support are also summarized in Table 2. The incidence of cardiac arrhythmia was significantly higher in the late RHF

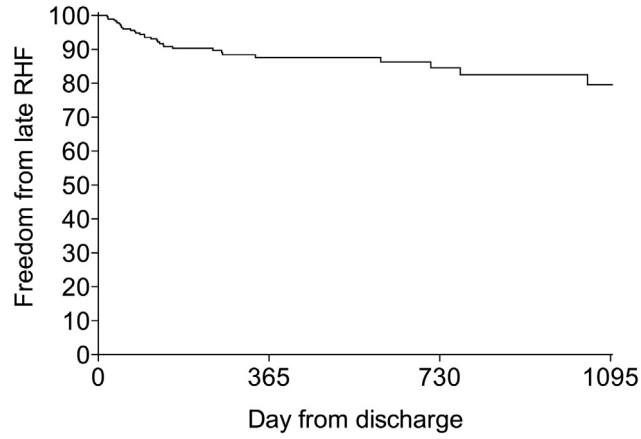

Figure 1 Freedom from late RHF rate for the entire cohort.

Table 1 Baseline Characteristics of Study Patients

	No RHF ($n = 260$)	RHF ($n = 33$)	p-value
Age (years)	56.6 ± 13.9	57.4 ± 13.3	0.76
Gender male	214 (82.3)	29 (87.9)	0.62
BSA (m^2)	1.94 ± 0.248	2.06 ± 0.217	0.0067
Body mass index	25.9 ± 5.24	28.3 ± 5.08	0.011
Hypertension	97 (37.3)	9 (27.3)	0.44
Diabetes mellitus	79 (30.4)	17 (51.5)	0.019
Hyperlipidemia	126 (48.5)	19 (57.6)	0.36
Ischemic cardiomyopathy	106 (40.8)	16 (48.5)	0.45
Intention to treat			0.68
Bridge to transplant	192 (73.8)	23 (69.7)	
Destination therapy	68 (26.2)	10 (30.3)	
ICD	202 (77.7)	29 (87.9)	0.26
Re-operative surgery	91 (35.0)	12 (36.4)	0.88
Pre-operative inotropic support	210 (80.8)	27 (81.8)	1.00
Pre-operative IABP support	66 (25.0)	6 (18.2)	0.52
Pre-operative mechanical circulatory support	22 (8.46)	2 (6.06)	0.68
Pre-operative ventilator support	11 (4.23)	2 (6.06)	0.25
LVEDD (mm)	69.6 ± 11.4	69.2 ± 10.6	0.83
LVEF (%)	14.7 ± 5.93	17.1 ± 6.81	0.049
Severely reduced RV systolic function	63 (24.2)	11 (33.3)	0.26
TR Grade III/IV (%)	45 (17.3)	8 (24.2)	0.34
CVP (mm Hg)	10.6 ± 5.33	11.3 ± 5.43	0.50
Mean PAP (mm Hg)	35.1 ± 9.70	35.1 ± 7.89	0.98
PCWP (mm Hg)	23.9 ± 7.95	23.7 ± 7.76	0.87
CI (liters/min/m^2)	1.64 ± 0.479	1.72 ± 0.644	0.44
CVP/PCWP ratio	0.479 ± 0.268	0.494 ± 0.205	0.76
PVR (Wood units)	4.01 ± 2.74	3.73 ± 2.42	0.60
Sodium (mmol/liter)	134 ± 4.20	135 ± 4.05	0.11
BUN (mg/dl)	33.2 ± 18.0	44.1 ± 20.5	0.0015
Creatinine (mg/dl)	1.47 ± 0.700	1.71 ± 0.527	0.059
Albumin (g/dl)	3.63 ± 0.520	3.67 ± 0.442	0.68
AST (IU/liter)	44.5 ± 90.6	35.3 ± 71.8	0.58
ALT (IU/liter)	56.1 ± 150	56.2 ± 198	0.99
Total bilirubin (mg/dl)	1.48 ± 1.17	1.23 ± 0.795	0.27
WBC (×1,000/ml)	8.52± 3.10	8.16 ± 3.18	0.54
Hemoglobin (g/dl)	11.5 ± 2.05	11.5 ± 1.74	0.93
Hct (%)	35.1 ± 5.80	36.0 ± 5.12	0.43
Platelets (×1,000/ml)	211 ± 71.6	205 ± 82.4	0.68
INR	1.37 ± 0.380	1.32 ± 0.319	0.47

Data expressed as mean ± SD or as number (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; BUN, blood urea nitrogen; CI, cardiac index; CVP, central venous pressure; Hct, hematocrit; IABP, intra-aortic balloon pump; ICD, implantable cardioverter-defibrillator; INR, international normalized ratio; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RV, right ventricular; WBC, white blood cells.

group. The incidence of device failure was similar between the groups. Device exchange was required in 4 (12%) patients in the late RHF group and 32 (12%) in the non-RHF group ($p = 1.00$).

Impact of late RHF on outcomes

The mean duration of LVAD support for the entire cohort after indexed hospital discharge was 438 days (range 5 to 3,066 days). Thirty-nine patients (13%) died on the device, 150 (51%) were bridged to transplantation, 99 (34%) remained on device support, and 5 (1.7%) showed native heart recovery enough to be weaned from the device. Duration of LVAD support was similar between the groups ($p = 0.14$).

The estimated on-device survival for the entire cohort was 89%, 80%, 77% and 58% at 1, 2, 3 and 4 years, respectively. Estimated on-device survival rates at 2 years were 73% in the RHF group and 82% in the non-RHF group ($p = 0.20$; Figure 2). However, overall survival at 2 years was significantly worse in patients who developed late RHF (60% vs 85%, $p = 0.016$; Figure 3).

Late RHF recurrence

In the RHF group, 15 patients (45%) had RHF recurrence at a median of 113 days after the first re-admission (range 8 to

Table 2 Intra-operative, Early and Late Post-operative Outcomes

	No RHF ($n = 260$)	RHF ($n = 33$)	p-value
Intra-operative variables			
Type of device [n (%)]			0.79
HeartMate II	224 (86.2)	28 (84.8)	
Others	36 (13.8)	5 (15.2)	
Concomitant procedure [n (%)]			
Tricuspid valve repair	53 (20.4)	5 (15.2)	0.64
Tricuspid valve replacement	4 (1.54)	3 (9.09)	0.033
Aortic valve repair	43 (16.5)	10 (30.3)	0.089
Prosthetic aortic valve closure	6 (2.31)	0 (0)	—
Aortic valve replacement	2 (0.769)	0 (0)	—
Mitral valve repair	41 (15.8)	1 (3.03)	—
Patent foramen ovale closure	15 (5.77)	3 (9.09)	—
Cardiopulmonary bypass time (min)	91.5 ± 42.6	95.8 ± 49.7	0.59
Aortic cross-clamp time (min)	6.51 ± 13.6	7.16 ± 12.5	0.81
Transfusion [n (%)]			
pRBC (units)	1.62 ± 2.36	1.31 ± 1.79	0.50
FFP (units)	2.90 ± 2.70	3.25 ± 2.61	0.49
PLT (units)	9.52 ± 7.09	8.63 ± 6.81	0.53
Nitric oxide use [n (%)]	99 (38.1)	14 (42.4)	0.71
Early morbidity			
ICU stay (days)	8.85 ± 7.45	8.64 ± 5.75	0.90
Hospital stay (days)	32.9 ± 37.2	35.2 ± 17.1	0.73
Major morbidity [n (%)]			
Stroke	10 (3.85)	3 (9.09)	0.17
Sepsis/bacteremia	5 (1.92)	2 (6.06)	0.18
Chest re-exploration for bleeding	32 (12.3)	7 (21.2)	0.17
Renal failure requiring CVVH	10 (3.85)	5 (15.2)	0.018
Ventricular arrhythmia	59 (22.7)	8 (24.2)	0.83
RVAD use	6 (2.31)	1 (3.03)	0.57
Late adverse event [number of patients (%)]			
Bleeding	63 (24.2)	6 (18.2)	0.52
LVAD-related infection	33 (12.7)	4 (12.1)	1.00
LVAD-unrelated infection	29 (11.2)	6 (18.2)	0.25
Atrial/ventricular tachyarrhythmia	24 (9.23)	10 (30.3)	0.0017
Stroke	23 (8.85)	4 (12.1)	0.52
Device failure	39 (15.0)	4 (12.1)	0.80
Device thrombosis	30 (11.5)	2 (6.06)	
Drive-line injury	5 (1.92)	1 (3.03)	
Bend relief disconnection	3 (1.15)	1 (3.03)	
Inflow malposition	1 (0.385)	0 (0)	

CVVH, continuous veno-venous hemofiltration; FFP, fresh frozen plasma; ICU, intensive care unit; LVAD, left ventricular assist device; PLT, platelets; pRBC, packed red blood cells; RVAD, right ventricular assist device.

938 days). Two patients had 4 re-admissions related to RHF. Freedom from second re-admission rate at 1 year was 44%. There was a trend for worse overall survival at 2 years in patients who developed late RHF recurrence compared with those who did not have recurrence (44% vs 75%, $p = 0.09$).

Outcomes according to intention to treat

We also examined the impact of late RHF on overall outcomes according to the intention to treat with either BTT or DT in each group. Pre-operatively, DT patients were more likely to be older (68 ± 10 vs 53 ± 13 years, $p < 0.0001$) and to have a smaller body surface area (1.9 ± 0.21 vs 2.0 ± 0.26 m^2, $p = 0.0067$), an ischemic etiology (55% vs 37%, $p = 0.0071$), a history of previous cardiac surgery (53% vs 29%, $p = 0.0003$), a higher sodium level (135 ± 3.8 vs 134 ± 4.3 mmol/liter, $p = 0.014$), higher blood urea nitrogen (40 ± 19 vs 33 ± 18 mg/dl, $p = 0.0037$) and lower total bilirubin (1.2 ± 0.71 vs 1.6 ± 1.2 mg/dl, $p = 0.0091$) compared with BTT patients. The incidence of late RHF was 13% ($n = 10$) in the DT population and 10% ($n = 23$) in the BTT population ($p = 0.67$).

In the BTT population, mean duration of LVAD support in the RHF group was significantly longer than that in the non-RHF group (465 ± 376 days vs 304 ± 301 days, respectively; $p = 0.0018$). Cardiac transplantation was successful in 12 of 23 patients (52%) in the RHF group compared with 138 of 192 patients (72%) in the non-RHF group ($p = 0.06$). Eleven of 12 patients (92%) received

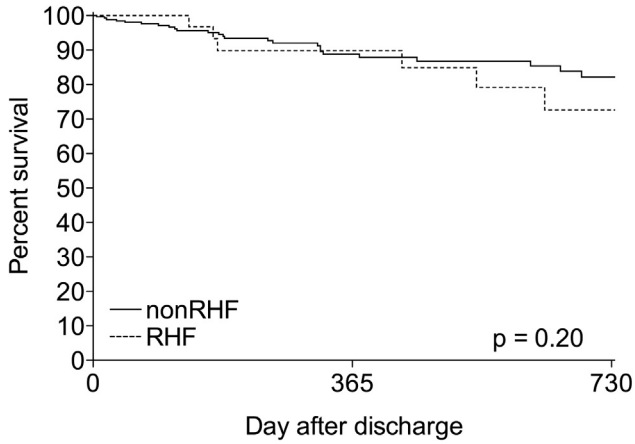

Figure 2 Comparison of estimated on-device survival: non-RHF group vs RHF group.

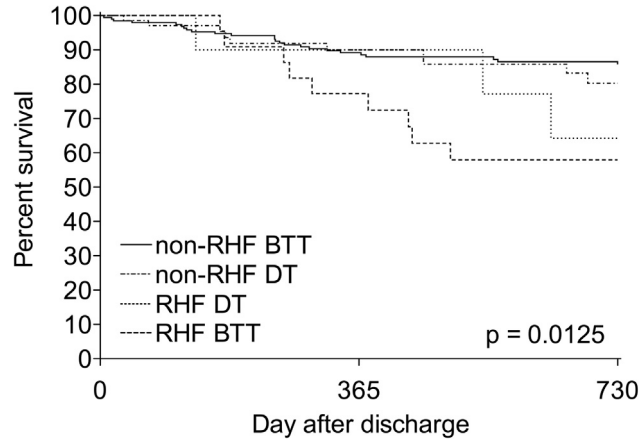

Figure 4 Overall survival stratified by intention to treat (BTT or DT) and late RHF development.

transplantation while in United Network of Organ Sharing Status 1A in the RHF group as compared with 88 of 138 (64%) in the non-RHF group ($p = 0.06$). Donor age (35 ± 7.2 vs 31 ± 11 years, $p = 0.27$) and BMI (28 ± 3.8 vs 27 ± 5.0, $p = 0.39$) were similar between the groups, whereas body surface area was significantly greater in the RHF group (2.1 ± 0.16 vs 1.9 ± 0.25 m^2, $p = 0.022$). The DT patients received LVAD support for an average of 737 days in the RHF group and 755 days in the non-RHF group ($p = 0.93$). Kaplan–Meier curves constructed for the 4 groups show that BTT patients in the RHF group had worse overall survival (Figure 4).

Risk factors for late RHF

According to the univariable Cox proportional hazards regression model, diabetes mellitus (HR 2.05, 95% CI 1.03 to 4.06, $p = 0.04$), BMI >29 (HR 2.47, 95% CI 1.24 to 4.94, $p = 0.01$) and blood urea nitrogen level >41 mg/dl (HR 2.19, 95% CI 1.10 to 4.36, $p = 0.025$) were significant predictors for late RHF.

Because renal function seems to be a key factor related to late RHF development, we examined the time course of renal function after LVAD implantation in each group (Table 3). Renal function was significantly restored 1 month after support initiation in both groups. However, the improvement had not been sustained throughout the support period in the RHF group. No significant differences were seen between baseline blood urea nitrogen and creatinine values and 6-month and 1-year values in the RHF group when compared with the non-RHF group. Post-operative renal function was significantly worse in the RHF group throughout the support period up to 1 year.

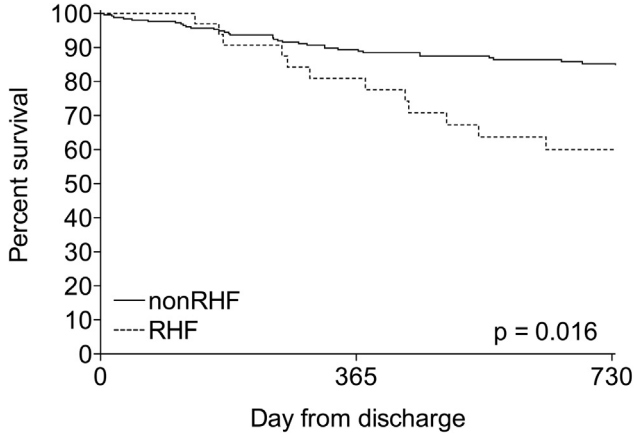

Figure 3 Comparison of overall survival: non-RHF group vs RHF group.

Discussion

The major findings of this study are as follows: (1) late RHF after LVAD implantation was common and persistent morbidity after continuous-flow LVAD implantation; and (2) late RHF had significant impact on overall survival, especially for the BTT population.

With the evolution of technology and improvements in patient management, use of continuous-flow pumps has grown rapidly. Significant improvements in survival have been reported from the INTERMACS.[5] Despite these successes, the issue of RHF after LVAD implantation remains unresolved. The development of RHF leads directly to early and late mortality.[5–8] To overcome this dilemma, studies have extensively examined RHF.[5–8] However, these published reports focused mostly on RHF occurring in the early post-operative period. The present data illuminate the paucity of evidence concerning long-term functional status after patients become stable enough with continuous-flow physiology.

From our results, RHF is a relatively common and persistent morbidity late after continuous-flow LVAD implantation. We found that 33 of 293 patients (11%) required re-admission related to RHF. Most (73%) were re-admitted within 6 months after implantation. Half of the patients had repeated admissions. The reported incidence of late RHF after continuous-flow LVADs is varied because a clear definition is lacking. Kormos et al reported that late RHF occurred in 33 of 484 patients (7%) with the HeartMate II LVAD.[6] However, they defined late RHF as reinstitution of inotropes >14 days after LVAD implantation. Hasin et al reported that 19 of 115 patients (17%) with

Table 3 Time Course of Renal Function During LVAD Support

	1 month			6 months			12 months		
	No RHF ($n = 258$)	RHF ($n = 31$)	p-value	No RHF ($n = 178$)	RHF ($n = 27$)	p-value	No RHF ($n = 104$)	RHF ($n = 22$)	p-value
BUN (mg/dl)	20.8 ± 10.3[a]	30.8 ± 18.6[a]	<0.0001	24.7 ± 11.9[a]	40.2 ± 17.5	<0.0001	24.8 ± 11.4[a]	38.6 ± 21.0	<0.0001
Creatinine (mg/dl)	1.11 ± 0.397[a]	1.44 ± 0.577[a]	<0.0001	1.27 ± 0.400[a]	1.74 ± 0.666	<0.0001	1.34 ± 0.522[a]	1.69 ± 0.662	0.0046

BUN, blood urea nitrogen; LVAD, left ventricular assist device; RHF, right heart failure.
[a] $p < 0.05$ vs baseline value in each group.

HeartMate II devices required re-admission related to recurrent heart failure.[9]

On the other hand, the incidence of late RVAD implantation was low (1%). The reported incidence of early RHF requiring RVAD support after LVAD insertion is 5% to 9%.[6–8] This discrepancy suggests that the etiologies of late RHF differ from those of early RHF. Late RHF can be related primarily to intrinsic right ventricular myocardial disease or can be secondary to various causes such as ventricular arrhythmia, progression of tricuspid regurgitation and pulmonary hypertension.[12] In the early phase after LVAD insertion, numerous transient factors, including acute geometric change of the right ventricle related to septal shifting, peri-operative acute kidney injury, infection and bleeding, could predispose patients to severe RHF, leading to the need for RVAD support.[6,13,14] These aggravating factors likely play an important role in developing early RHF requiring RVAD support. The low incidence of RVAD may also reflect a high threshold for RVAD insertion because of surgical complexity (e.g., re-operation, venous congestion) and a lack of available durable devices.

Multiple studies have identified risk factors for the development of early RHF after LVAD implantation, but little information exists regarding predictors for late RHF. Identifying these risk factors is clinically relevant because planned biventricular assist device implantation may result in better outcomes, especially for the high-risk BTT population.[15] Interestingly, compared with the non-RHF group, our RHF cohort had similar hemodynamic indices, including CVP and CVP/PCWP ratio. In general, these variables are representative markers for intrinsic right ventricular dysfunction.[6,16] Kormos et al reported findings similar to ours in that patients who developed late RHF had similar CVP and CVP/PCWP values to those who did not have any RHF, whereas patients who developed early RHF had significantly higher CVP and CVP/PCWP values compared with the non-RHF population.[6] From these results, pre-operative hemodynamic indices do not seem to be sensitive enough to detect late RHF after placement of a continuous-flow LVAD. Once the patient and his/her right ventricle adapt to new physiology under the continuous-flow pump, factors other than intrinsic right ventricular dysfunction may trigger RHF development. Indeed, patients in the RHF group more frequently required re-admission due to cardiac tachyarrhythmia that may lead to worsening right ventricular function.[17] Other adverse events, including infection and device failure, were also common during long-term LVAD support. These late adverse events may contribute to the development of late RHF as a chronic aggravating factor.

Our risk-factor analysis has demonstrated that higher BMI and higher blood urea nitrogen level were key factors for late RHF development. This result is somewhat consistent with previous findings. A previous study of a large cohort demonstrated that patients with higher BMI had higher re-admission rates due to bleeding, infection and respiratory failure, all of which can exacerbate right ventricular function during LVAD support.[18] Furthermore, obesity can be a cause of not only left ventricular

dysfunction but also right ventricular dysfunction (obesity cardiomyopathy).[19] Patients with high BMIs may have a component of this pathophysiology and, therefore, may represent a high-risk cohort for development of RHF. Higher blood urea nitrogen level was associated not only with higher early RHF incidences but also with higher re-admission rates from all causes after continuous-flow LVAD implantation.[6,10] In most patients undergoing LVAD implantation, renal dysfunction is likely reversible.[20] However, one recent study demonstrated that improved renal function after mechanical circulatory support was largely transient and not necessarily indicative of an improved prognosis.[21]

Our study data from the RHF group show a similar trend. Improved renal function at 1 month returned to baseline level at 6 months as compared with the non-RHF group. It is easy to speculate that volume management is more difficult in patients with sustained renal dysfunction. Inadequate volume control could result in RHF even with adequate LVAD support. On the other hand, RHF could also trigger renal malperfusion related to decreased flow to the LVAD pump and increased venous pressure. Thus, late RHF development and worsening of renal function are closely linked for cause and effect. A further study with a larger cohort is required to improve our understanding of the relationship between late RHF development and renal function after continuous-flow LVAD implantation.

Another important finding from our study is the impact of late RHF on survival. Despite the need for frequent re-admission, the late RHF group had similar on-device survival to the non-RHF group. However, patients with late RHF had a 25% reduction in 2-year overall survival compared with patients who did not have late RHF. Subgroup analysis revealed that this reduction was mostly attributed to worse overall outcomes in the BTT population. This phenomenon can be explained by the fact that patients with late RHF had a history of diabetes mellitus, large body habitus and more advanced renal dysfunction. All of these are significant risk factors for post-transplant mortality.[22,23] The current study raises a simple question as to whether patients with multiple re-admissions related to late RHF should be transplanted more urgently or whether they should not be transplanted in consideration of the chronic donor shortage. Further multicenter studies on larger populations are warranted to answer this question.

There are several limitations to our study. First, it was a retrospective analysis of a single center's experience. However, the strength of this study was the large number of patients to whom consistent strategies were applied in terms of patient selection, operative procedure and post-operative management. Second, the number of patients in the late RHF group was low, thereby limiting statistical power. Third, because of the lack of a standard definition of late RHF, we defined RHF as an incident requiring re-admission after indexed hospital discharge, because frequent re-admission after LVAD insertion remains a clinically relevant issue.[9,10] The numbers of patients who had mild RHF symptoms and were treated as outpatients were not recorded; thus, the overall incidence may be underestimated. Furthermore, RHF can be aggravated by ventricular arrhythmia, infection and device failure. Although each one of these is a different pathologic entity for treatment, there is a certain interaction between these pathologies and the occurrence of RHF. Therefore, the clear-cut definition of primary or secondary RHF seems difficult. Prospective data collection under unified criteria is desirable to confirm or extend our findings.

In conclusion, late RHF is a relatively common and persistent morbidity after continuous-flow LVAD implantation. Late RHF does not affect survival during LVAD support. However, its occurrence is associated with worse overall outcomes, especially in the BTT population.

Disclosure statement

Y.N. has received consulting fees from Thoratec Corp. The remaining authors have no conflicts of interest to disclose.

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