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Hemodynamic Assessment of Patients With and Without Heart Failure Symptoms Supported by a Continuous-Flow Left Ventricular Assist Device

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Abstract

Objective: To investigate differences in invasive hemodynamic parameters and outcomes in patients with and without heart failure (HF) symptoms after left ventricular assist device (LVAD) implantation.

Patients and Methods: We performed a single-center retrospective analysis of 51 symptomatic patients and 50 patients with resolved HF symptoms who underwent right-sided heart catheterization (RHC) after LVAD implantation from March 1, 2007, through June 30, 2016. Patient characteristics and outcomes including all-cause mortality and right ventricular (RV) failure were compared between groups.

Results: Fifty-one patients had development of HF symptoms after LVAD implantation and underwent RHC a mean ± SD of 243.7±288 days postoperatively. Fifty asymptomatic LVAD recipients underwent routine RHC 278.6±205 days after implantation. Compared with patients who had resolved HF symptoms, symptomatic patients were older, more likely to be male, and more likely to have ischemic cardiomyopathy. Symptomatic patients had higher right atrial pressure ($P<.001$), mean pulmonary arterial pressure ($P<.001$), and pulmonary capillary wedge pressure ($P<.001$). Improvements in right atrial pressure, mean pulmonary arterial pressure, and pulmonary capillary wedge pressure before and after LVAD implantation were less remarkable in symptomatic patients. The frequency of RV dysfunction was significantly higher among symptomatic patients than patients with resolved HF symptoms ($P=.001$). Symptomatic patients displayed significantly higher risk of all-cause mortality (hazard ratio, 3.0; 95% CI, 1.3-6.5; $P=.007$) and RV failure (hazard ratio, 6.2; 95% CI, 1.3-29.7; $P=.02$) independent of other predictors of outcome.

Conclusion: Patients with recurrent HF symptoms after LVAD implantation display more profound hemodynamic derangements, greater burden of RV failure, and increased rates of all-cause mortality compared with LVAD recipients with resolved HF symptoms.

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Left ventricular assist devices (LVADs) provide hemodynamic support for selected patients with advanced heart failure (HF). More than 15,000 LVADs have been implanted in the United States, with more than 2000 LVADs implanted annually.[1] As a result of improved durability and survival, the eligible patient population has expanded to include less critically ill patients with longer support times. Therefore, the focus has now shifted toward identification and management of complications associated with long-term LVAD support. Unlike previous pulsatile devices that were preload responsive, continuous-flow LVADs have a fixed pump speed that does not change with

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exercise, selected to unload the left ventricle (LV) without causing excessive emptying (suction events) and right ventricular (RV) overload. Resting and exercise hemodynamics of LVAD recipients are usually improved, with lower mean pulmonary arterial pressure (mPAP) and pulmonary capillary wedge pressure (PCWP) and higher cardiac index. However, complications such as RV dysfunction, aortic regurgitation, arrhythmias, or pump thrombosis may lead to recurrent symptoms of HF.[2]

New or recurrent HF symptoms can occur in LVAD recipients as a result of RV dysfunction, left-sided dysfunction, or both. Right ventricular dysfunction is considered the most common cause of recurrent HF after LVAD implantation. In the HeartMate II Destination Therapy clinical trial, late RV failure, defined as requiring inotropic support starting 14 days or later after implantation, occurred in 7% of patients.[3] Distorted RV geometry, progression of chronic RV dysfunction, tricuspid valve regurgitation, pump thrombosis or malfunction, recurrent ventricular arrhythmias, tamponade, and persistent pulmonary hypertension can also lead to HF after LVAD implantation.[4] In these cases, hemodynamic assessment with right-sided heart catheterization (RHC) usually provides valuable diagnostic and prognostic information and guides further therapeutic strategies.

We sought to investigate the hemodynamic profiles of patients with recurrent HF after LVAD implantation and evaluate the prognosis and incidence of major postoperative complications.

PATIENTS AND METHODS

Our study protocol was approved by the Institutional Review Board of Mayo Clinic College of Medicine and Science. We identified 294 adult patients (aged ≥18 years) with end-stage HF who received a US Food and Drug Administration–approved LVAD from March 1, 2007, through June 30, 2016, for either destination therapy (DT) or bridge to transplant (BTT) at Mayo Clinic in Rochester, Minnesota, and were supported for at least 3 months. From this cohort, we identified 51 consecutive patients who had development of new-onset signs and symptoms of HF occurring after LVAD implantation following recovery from the perioperative period and the development of an asymptomatic status. Symptoms were defined as new-onset dyspnea, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, abdominal pain, fatigue, or weakness. We excluded patients who presented with symptoms of new-onset shortness of breath due to pneumonia, exacerbation of chronic obstructive pulmonary disease, other interstitial lung disease, or pulmonary embolism.

This group of symptomatic patients was compared with 50 LVAD recipients with resolved HF symptoms who had undergone implantation during the study period. All patients in both groups underwent RHC, either for worsening symptoms in the first group or for optimization of LVAD settings. Post-LVAD RHC is not mandatory at our institution but is encouraged for symptomatic patients and is at the treating cardiologist's discretion. All patients received continuous-flow LVADs—HeartMate II (Abbott-Thoratec) or HeartWare HVAD (Medtronic), which are contemporary durable devices. Patients who required temporary left-sided mechanical circulatory support, biventricular assist device, or total artificial heart were excluded from the analysis.

Clinical and Demographic Data

Demographic, clinical, echocardiographic, LVAD, and laboratory data were obtained from the Mayo Clinic College of Medicine and Science collected clinical database. The estimated glomerular filtration rate was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.

Outcomes

The primary outcome studied was all-cause mortality. Secondary outcomes included (1) RV failure, (2) suspected or confirmed pump thrombosis, (3) thromboembolic stroke or transient ischemic attack, (4) gastrointestinal bleeding, (5) LVAD driveline or pump infection (based on the Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] criteria, see "Definitions" section). Survival and clinical events information was obtained from subsequent clinic visits and written correspondence from local physicians.

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Moreover, we assessed hemodynamic parameters including mean arterial pressure, right atrial pressure (RAP), mPAP, PCWP, the maximal rate of rise in RV pressure (RV dP/dtmax), dP/dtmax, transpulmonary gradient, cardiac output and cardiac index based on thermodilution, pulmonary vascular resistance, RV stroke work index, RAP:PCWP ratio before and after LVAD implantation.

Right-Sided Heart Catheterization

Right-sided heart catheterization was performed via the internal jugular, femoral, or brachial vein access using the modified Seldinger technique. Pulmonary end-expiratory pressures were measured with a balloon-tipped catheter at steady state with the patient in a supine position. Mean arterial pressure was calculated as 1/3 × systolic blood pressure + 2/3 × diastolic blood pressure in the case of invasive measurement or based on Doppler technique in the case of noninvasive measurement. Pulmonary vascular resistance was determined using the following equation: 80 (mPAP − PCWP)/cardiac output. Right ventricular stroke work index was calculated as (cardiac index/heart rate) × (mPAP − RAP) × 0.0136.

Echocardiography

Postoperative echocardiography was performed monthly and as needed in our LVAD population at each outpatient visit or when clinically indicated. The assessment of RV function was based on the recommendations of the American Society of Echocardiography. A qualitative 4-point scale score—none, mild, moderate, severe—was used to describe RV dysfunction.[5]

Definitions

All adverse events were defined according to the standard INTERMACS definition used during the time period of implantation. Right ventricular failure was defined as central venous pressure or RAP greater than 16 mm Hg and/or requiring postimplant inotropes for RV support. Criteria for suspected pump thrombosis included elevation of lactate dehydrogenase concentration in addition to other clinical findings of hemolysis, including recent arterial thromboembolic event, symptoms of HF confirmed with abnormal hemodynamic findings, and presence of abnormal pump variables, or pump function.

Statistical Analyses

Statistical analysis was performed using SPSS Inc statistical software, version 23. All variables were tested for normal data distribution. Normally distributed data were expressed as mean ± SD. Nonnormally distributed data were presented as the median with the interquartile range. Patient characteristics were compared using the χ^2 test or the Fisher-Freeman-Halton exact test for categorical variables, the independent *t* test for normally distributed continuous variables, and the Kruskal-Wallis test for continuous variables with skewed distribution. Paired *t* tests were used for comparisons between pre-LVAD and post-LVAD hemodynamics. A Cox regression model, with adjustment for clinically significant factors (age, continuous variable; ischemic cardiomyopathy, categorical variable; postoperative RAP, continuous variable), was fit to determine the factors associated with the main outcomes of our study. Patients were censored at the termination of LVAD therapy because of device explantation or heart transplant. Variables with $P<.05$ of significance in univariate analyses were entered into multivariate analyses after the confirmation that there was no significant multicollinearity among them (variance inflation factor <5 was considered nonsignificant). All significance tests were 2-tailed and conducted at the 5% significance level.

RESULTS

The study cohort consisted of 101 patients who underwent LVAD implantation (82 [81.2%] with a HeartMate II and 19 [18.8%] with a HeartWare HVAD), either as BTT (45 [44.6%]) or DT (56 [55.4%]). The median age at the time of implant was 61.6 years (range 32.5-77). All patients had end-stage HF and were classified as INTERMACS Profile 1 (23 [22.8%]), 2 (25 [24.7%]), 3 (20 [19.8%]), 4 (26 [25.7%]), 5 (4 [4.0%]), or 6 (3 [3.0%]).

Fifty-one patients had development of symptoms after LVAD implantation and underwent RHC a mean ± SD of 243.7±288 days postoperatively. Fifty LVAD recipients with resolved HF symptoms underwent routine RHC 278.6±205 days postimplantation ($P=.50$ vs symptomatic patients). Compared

TABLE 1. Clinical and Demographic Characteristics of 101 Study Patients With and Without HF Symptoms[a,b,c]

Variable	Symptomatic patients (n=51)	Patients with resolved HF symptoms (n=50)	*P* value
Age (y)	62.2±8.8	55.7±11.1	.003
Males	45 (88.2)	34 (68.0)	.02
Device			.80
HeartMate II (Abbott-Thoratec)	42 (82.4)	40 (80.0)	
HeartWare HVAD (Medtronic)	9 (17.6)	10 (20.0)	
Type of support			.30
Destination therapy	31 (60.8)	25 (50.0)	
Bridge to transplant	20 (39.2)	25 (50.0)	
INTERMACS class			.15
1	12 (23.5)	11 (22.0)	
2	8 (15.7)	17 (34.6)	
3	11 (21.6)	9 (18.0)	
4	16 (31.4)	10 (20.0)	
5	1 (2.0)	3 (6.0)	
6	3 (7.7)	0	
Hypertension	27 (52.9)	22 (40.0)	.40
Diabetes mellitus	19 (37.3)	15 (30.0)	.50
Ischemic cardiomyopathy	26 (51.0)	13 (26.0)	.009
Body surface area (m^2)	2.04±0.25	1.98±0.2	.20
Device speed (rpm)			
HeartMate II	9438±515	9460±304	.50
HeartWare	2617±90	2716±159	.01
NT-proBNP (pg/mL)			
Pre-LVAD	7236±8019	7463±7322	.70
Post-LVAD	6467±7333	2318±2813	<.001
Estimated GFR (mL/min/1.73 m^2)	47±17.3	56±26.4	.09
Creatinine (mg/dL)	1.63±0.8	1.34±0.5	.05
LDH (U/L)	406±811	429.8±664	.06
Albumin (g/dL)	3.77±0.5	3.74±0.5	.70
Preoperative echocardiographic right ventricular dysfunction	2.3±1.3	2.48±1.1	.70
Cardiopulmonary bypass time (min)	119.8±45	103.4±45	.07
Transplant	4 (7.8)	9 (18.0)	.10
Tricuspid valve surgery at time of implant	16 (51.0)	26 (52.0)	.50
Aortic valve surgery at time of implant	5 (9.8)	9 (18.4)	.30
Days to RHC post LVAD implantation	243.7±288	278.6±205	.50
Duration of support (y)	3.16±2.6	3.47±2.1	.30

[a]GFR = glomerular filtration rate; HF = heart failure; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LDH = lactate dehydrogenase; LVAD = left ventricular assist device; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RHC = right-sided heart catheteration.

[b]Data are presented as No. (percentage) of patients or mean ± SD.

[c]SI conversion factors: To convert NT-proBNP values to ng/L, multiply by 1.0; to convert creatinine values to μmol/L, multiply by 88.4; to convert LDH values to μkat/L, multiply by 0.0167; to convert albumin values to g/L, multiply by 10.

with patients with resolved HF symptoms, symptomatic individuals were older, more likely to be male, and more likely to have ischemic cardiomyopathy (Table 1). Preoperative renal function was nonsignificantly lower in symptomatic patients compared with patients with resolved HF symptoms (estimate GFR 47 ± 17.3 vs 56 ±26.4; *P*=.09). Before LVAD implantation, N-terminal pro-B-type natriuretic peptide levels were higher than after LVAD but were similar between the 2 groups, whereas after LVAD implantation, patients who had development of HF symptoms had higher N-terminal pro-B-type natriuretic peptide levels at the time of post-LVAD RHC (6467±7333 pg/mL vs 2318±2813 pg/mL [to convert to ng/L, multiply by 1.0] in symptomatic patients vs patients with resolved HF symptoms, respectively; *P*<.001). The distribution of INTERMACS categories, the frequency of concomitant tricuspid or aortic

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TABLE 2. Differences in Hemodynamic Parameters of LVAD Recipients With and Without HF Symptoms[a]

Hemodynamic parameters	Symptomatic patients (n=51)			Patients with resolved HF symptoms (n=50)			*P* value for pre-LVAD in patient with vs without HF symptoms	*P* value for post-LVAD in patient with vs without HF symptoms
	Pre-LVAD	Post-LVAD	*P* value	Pre-LVAD	Post-LVAD	*P* value		
Mean arterial pressure (mm Hg)	75.2±11.8	82.3±14.8	.07	73.1±9.2	81.7±14.2	.005	.40	.90
Mean right atrial pressure (mm Hg)	15.8±6.4	15.6±7.2	.99	14.1±6	9.9±5.2	.001	.20	<.001
Mean pulmonary arterial pressure (mm Hg)	36.7±9.4	29.7±10.3	<.001	37.9±9.8	22.6±7	<.001	.60	<.001
Mean capillary wedge pressure (mm Hg)	22.3±6.6	17.7±9.3	<.001	24.8±7.5	11.3±6.1	<.001	.10	<.001
Transpulmonary gradient (mm Hg)	14.5±6.7	12.1±6.4	.03	13.1±6	11.1±4.1	.03	.30	.40
Cardiac output (L/min)	3.7±1.2	5.0±1.1	.001	3.8±1.1	5.2±1.3	.01	.98	.60
Cardiac index (L/min/m^2)	1.8±0.5	2.4±0.5	.001	1.6±0.9	2.5±0.4	.005	.70	.60
Right ventricular dP/dT (mm Hg/s)	410±228	430±297	.80	516±320	585±364	.07	.60	.05
Right ventricular stroke work index (g/m^2/beat)	7.8±4.3	6.6±4	.03	7.9±3.8	5.7±2.9	<.001	.90	.20
Pulmonary vascular resistance (Wood units)	3.9±2	2.4±1.1	<.001	3.6±1.9	2.5±1	.002	.40	.80
Right atrial to pulmonary capillary wedge pressure ratio	0.71±0.25	1.0±0.4	.007	0.57±0.21	0.90 ±0.3	<.001	.003	.20

[a]HF = heart failure; LVAD = left ventricular assist device.

valve surgery at the time of implant, and the frequency of preoperative RV dysfunction did not differ between the 2 groups (Table 1).

Hemodynamic Assessment

At baseline before LVAD implantation, no significant differences in hemodynamic parameters between symptomatic patients and patients with resolved HF symptoms were noted with the exception of the RAP:PCWP ratio, which was significantly higher in the symptomatic patients (0.71±0.25 vs 0.57±0.21; *P*=.003) (Table 2). After LVAD implantation, symptomatic patients had significantly higher RAP, mPAP, and PCWP (all *P*<.001) but had similar cardiac output and cardiac index compared with patients with resolved HF symptoms (Figure 1).

In the subgroup analysis of DT patients, RAP (14±5.8 vs 9.7±5.5; *P*=.007), mPAP (27.8±7.2 vs 22.4±7.5; *P*=.006), and PCWP (15.5±6.2 vs 11.9; *P*=.02) were significantly higher while cardiac index was similar (2.4±0.5 vs 2.4±0.4; *P*=.90) in symptomatic patients vs patients with resolved HF symptoms. Similarly, in BTT patients, symptomatic status was associated with significantly higher RAP (18.2±8.7 vs 10±5; *P*=.001), mPAP (32.9±13.6 vs 22.8±6.5; *P*=.005), and PCWP (21.5±12.4 vs 10.8±5.7; *P*=.004) and similar cardiac index (2.5±0.5 vs 2.6±0.4; *P*=.80) compared with patients with resolved HF symptoms.

Among the 51 symptomatic patients, the frequency of RV dysfunction (defined as RAP >16 mm Hg, RAP:PCWP ratio >1, and cardiac index <2.2 L/min per m^2)[3,4] was significantly higher compared with the 50 asymptomatic patients (19 [37.0%] vs 9 [18.0%]; *P*=.001) (Table 3). The frequency of mixed RV dysfunction and increased left-sided pressures (PCWP >18 mm Hg, RAP >16 mm Hg, and cardiac index <2.2 L/min per m^2) suggestive of inadequate LV unloading was seen in twice as many symptomatic patients (7 [13.0%] vs 3 [6.0%]). Finally, 38 patients with resolved HF symptoms (76.0%) had normal hemodynamic profiles vs 20 (39.1%) in symptomatic patients (*P*<.001).

Outcomes

The median follow-up time was 2.7 years (range, 0.2-8.2 years). The primary end point

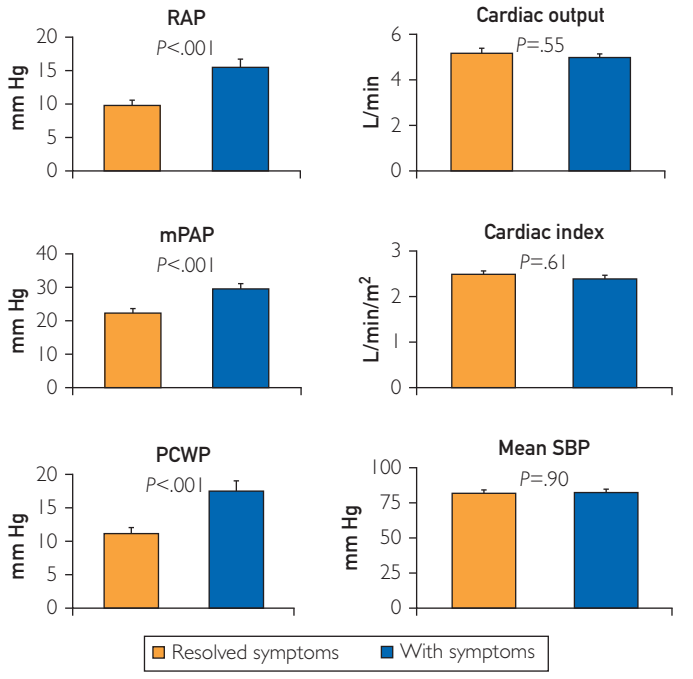

FIGURE 1. Differences in hemodynamics between patients with heart failure symptoms and those with resolved heart failure symptoms after LVAD implantation. Bars represent the mean ± SEM of right atrial pressure (RAP), mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), cardiac output, cardiac index, and mean systemic blood pressure (SBP) measurements.

of all-cause mortality occurred in 33 of the 51 symptomatic patients (64.7%) and 10 of the 50 patients with resolved HF symptoms (20.4%) (*P*<.001) (Figure 2). Among symptomatic patients, 12 (36.4%) died of multiorgan failure, 11 (33.3%) of intracranial bleeding, 2 (6.1%) of HF, and 2 (6.1%) of stroke or pump thrombosis. In patients with resolved HF symptoms, the most frequent causes of death were stroke and/or pump thrombosis (3 [30.0%]), respiratory failure (2 [20.0%]), or multiorgan failure (4 [40.0%]). The time from the post-LVAD RHC to death was 2.0±2.1 years in symptomatic patients and 3.5±1.4 years in patients with resolved HF symptoms. Among symptomatic patients, 4 (7.8%) underwent heart transplant vs 19 (18.0%) in patients with resolved HF symptoms (*P*=.10).

On unadjusted Cox proportional hazards modeling, the presence of symptoms was associated with increased all-cause mortality (hazard ratio [HR], 3.0; 95% CI, 1.4-6; *P*=.003) (Table 4). Right ventricular failure occurred in 16 symptomatic patients (31.4%) and 2 LVAD recipients with resolved HF symptoms (4.1%) (HR, 7.0; 95% CI, 1.6-30.0; *P*=.009). However, support with an RV assist device (RVAD) was required in 3 symptomatic patients (5.9%) and 2 patients with resolved HF symptoms (4.0%) (log-rank χ^2, 0.160; *P*=.70). Pump thrombosis occurred in 10 symptomatic patients (19.6%) and 13 patients with resolved HF symptoms (26.0%) (log-rank χ^2, 0.75; *P*=.40). Symptoms of HF were not associated significantly with stroke/transient ischemic attacks (log-rank χ^2, 0.12; *P*=.70), gastrointestinal bleeding (log-rank χ^2, 3.7; *P*=.06), and driveline/pump infections (log-rank χ^2, 0.20; *P*=.90).

We constructed Cox proportional hazards models with age, presence of ischemic cardiomyopathy, and postoperative RAP and found that symptomatic status remained associated with significantly higher risk of all-cause mortality (adjusted HR, 3.0; 95% CI, 1.3-6.5; *P*=.007) and RV failure (adjusted HR, 6.2; 95% CI, 1.3-29.7; *P*=.02).

TABLE 3. Distribution of Various Patterns of Hemodynamic Abnormalities in LVAD Recipients With and Without HF Symptoms[a,b]

Hemodynamic abnormalities	Symptomatic patients (n=51)	Patients with resolved HF symptoms (n=50)	*P* value
Normal hemodynamics	20 (39.2)	38 (76.0)	<.001
Mixed ventricular failure	7 (13.7)	3 (6.0)	
Left ventricular failure	5 (9.8)	0	
Right ventricular failure	19 (37.3)	9 (18.0)	

[a]HF = heart failure; LVAD = left ventricular assist device.
[b]Data are presented as No. (percentage) of patients.

DISCUSSION

We assessed hemodynamic parameters and outcome of patients with and without HF symptoms after LVAD implantation. The salient findings of our study may be summarized as follows: (1) in a cohort of patients with HF symptoms after LVAD implantation and asymptomatic LVAD recipients who underwent routine hemodynamic assessment, symptomatic status was associated with higher RAP, mPAP, PCWP, and similar cardiac output and cardiac index compared with patients with resolved HF symptoms, and (2) HF symptoms were associated with higher

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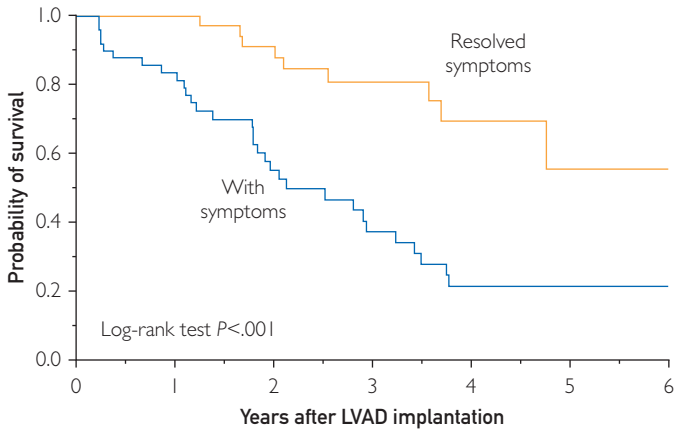

No. at risk							
Resolved symptoms	50	42	29	19	11	5	2
With symptoms	51	38	22	12	8	6	5

FIGURE 2. Kaplan-Meier estimates of overall survival in patients with heart failure symptoms and those with resolved heart failure symptoms while on LVAD support. Patients with symptoms had significantly lower overall survival compared with patients with resolved symptoms ($P<.001$ by log-rank test).

all-cause mortality and RV failure after LVAD implantation.

Persistent HF symptoms early after LVAD implantation are not uncommon, occurring in up to one-fourth of patients[2-4] depending on the definition used. Right ventricular failure, defined as the requirement for an RVAD or continued use of inotropes more than14 days after implantation, is usually the most common cause of early postoperative HF. Preoperative RV dysfunction, excessive volume resuscitation and transfusion, perioperative RV injury due to prolonged cardiopulmonary bypass time, misalignment of the LVAD inflow cannula, and LVAD thrombosis are the main causes of early RV failure, which is associated with increased duration of hospital stay, major bleeding, renal failure, need for reoperation, poor outcomes posttransplant, and increased mortality.[2]

Late onset of HF after successful LVAD implantation is also common, but the incidence is uncertain. Late-onset HF after LVAD implantation can be due to primarily RV, primarily left-sided, or mixed biventricular failure from LVAD-associated or non—LVAD-associated causes. In the setting of LVAD support, LV unloading decreases LV size and leads to distortion of the geometry of the RV, resulting in septal bowing. This septal bowing can in turn cause obstruction to RV outflow as well as decreased RV stroke volume and worsening tricuspid regurgitation.[5] However, LVAD support also decreases pulmonary artery pressures and RV afterload and results in augmented RV performance. Support with continuous-flow LVADs has been found to improve RV function and decrease RA pressures independent of device speed.[6] Left-sided HF can occur as a consequence of LVAD thrombosis, aortic regurgitation, obstruction of the LVAD inflow or outflow cannula (as a result of kinking or, rarely, thrombosis), motor dysfunction, or driveline fracture, which lead to inadequate LV unloading or worsening mitral regurgitation, diminished LVAD pump output, and inadequate forward flow. Non—LVAD-associated causes of late-onset HF are cardiac tamponade, persistent pulmonary hypertension, pulmonary embolism, and anemia due to gastrointestinal bleeding or recurrent ventricular arrhythmias.

In our patient cohort, we identified 8 cases of persistent precapillary pulmonary hypertension as the cause of HF and no cases of late cardiac tamponade or pulmonary embolism. Symptomatic patients had higher but not significantly different pulmonary vascular resistance. Pulmonary hypertension, which is

TABLE 4. Impact of Recurrent HF Symptoms on All-Cause Mortality, Right Ventricular Dysfunction, Pump Thrombosis, Gastrointestinal Bleeding, Stroke, and Driveline Infections After LVAD Implantation[a,b]

Outcome	Hazard ratio for symptoms of HF	95% CI	*P* value
All-cause mortality			
Unadjusted	3.0	1.4-6.0	.003
Adjusted	3.0	1.3-6.5	.007
Right ventricular failure			
Unadjusted	7.0	1.6-30.0	.009
Adjusted	6.2	1.3-29.7	.02
Pump thrombosis			
Unadjusted	0.7	0.3-1.6	.40
Adjusted	1.2	0.5-3.2	.70
Gastrointestinal bleeding			
Unadjusted	2.0	0.97-4.1	.06
Adjusted	2.2	0.98-4.8	.05
Stroke/transient ischemic attack			
Unadjusted	1.3	0.3-5.6	.70
Adjusted	1.9	0.2-14.5	.60
Driveline/pump infections			
Unadjusted	1.1	0.4-2.7	.90
Adjusted	1.2	0.4-3.5	.70

[a]HF = heart failure; LVAD = left ventricular assist device.
[b]Adjusted for age, presence of ischemic cardiomyopathy, and postoperative right atrial pressure.

frequently encountered in the advanced HF population, improves significantly after LVAD implantation, even when defined as fixed before ventricular assist device implantation.[7] Patients with persistent pulmonary hypertension after LVAD implantation are at risk for RV failure resulting from sustained RV afterload in the setting of increased RV preload and preexisting RV dysfunction. Treatment with phosphodiesterase-5 inhibitors or endothelin receptor antagonists may improve pulmonary hemodynamics in these patients,[8] but it is unclear whether there is any clinical benefit.

In the absence of other etiologies, progressive RV dysfunction is treated initially with device optimization under echocardiographic guidance of invasive hemodynamic evaluation and diuresis. Reinstitution of inotropic support may be necessary in cases of advanced RV dysfunction, but it is associated with higher burden of arrhythmias, line infections, and thrombosis without robust improvement of patients' symptoms. In BTT but not DT patients, RV support with a durable RVAD is indicated for refractory severe HF. Therefore, identification of patients who are at higher risk for postoperative RV failure should be an integral part of pre-LVAD evaluation. Despite the availability of several different risk scores,[9-14] RV failure after LVAD implantation has proved difficult to predict, and currently there is no consensus on how best to predict early or late right-sided HF in the this population.

Previous studies have suggested that a large portion of LVAD patients have abnormal hemodynamics including elevated filling pressures and reduced cardiac index, despite the absence of symptoms or adjustment of the speed based on conventional echocardiographic criteria such as interventricular septum position, aortic valve opening, and mitral regurgitation. Optimization of device speed based on hemodynamic ramp study has been shown to effectively unload the LV and normalize PCWP and central venous pressure.[15,16] Among patients with HeartMate III enrolled in a small multicenter study, invasive optimization resulted in improvement of hemodynamic parameters in 81.3% of the participants within a narrow speed range.[16] Moreover, this study also found that patients with lower baseline cardiac output had a reduced response to speed increase.

At Mayo Clinic, after the completion of the current study we employed a stepwise approach for patients with recurring HF symptoms and abnormal hemodynamics: first, echocardiography-guided adjustment of speed, assessment for presence of aortic regurgitation and RV dysfunction, and optimization of diuretic regimen is attempted. If these measures fail to alleviate symptoms, invasive hemodynamic ramp study is performed, speed is adjusted to the level associated with normalization of RA, PCW, and cardiac index, and the need for inotropic support is addressed. However, similar to the findings of previous studies,[14,15] a percentage of patients remain outside normal hemodynamic range despite speed optimization and medical therapy. The deranged hemodynamics and greater mortality in symptomatic patients observed in this study does not prove that efforts to optimize hemodynamics are effective in LVAD recipients, but the documented improvements in hemodynamics that can be achieved certainly support this approach. Further prospective study is required to test the value of LVAD optimization using invasive and noninvasive parameters.

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The main limitation of our study is its retrospective design and sample size. An additional limitation of this study is that it represents the experience of a single center where most of the patients were implanted with HeartMate II LVAD as DT; thus, results might not be generalizable to other health systems with different patients characteristics and using different continuous-flow LVADs. However, despite these limitations, our data provide a comprehensive hemodynamic assessment of symptomatic patients after LVAD implantation.

CONCLUSION

Recipients of LVADs who have recurrent symptoms of HF display an adverse hemodynamic profile that is associated with adverse outcomes and greater burden of RV dysfunction. These data suggest that thorough evaluation of the RV failure risk and preoperative hemodynamic optimization is vital for LVAD candidates.

Abbreviations and Acronyms: **BTT** = bridge to transplant; **DT** = destination therapy; **HF** = heart failure; **HR** = hazard ratio; **INTERMACS** = Interagency Registry for Mechanically Assisted Circulatory Support; **LV** = left ventricle; **LVAD** = left ventricular assist device; **mPAP** = mean pulmonary arterial pressure; **PCWP** = pulmonary capillary wedge pressure; **RAP** = right atrial pressure; **RHC** = right-sided heart catheterization; **RV** = right ventricular; **RVAD** = RV assist device

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