ORIGINAL RESEARCH

Predictors and Clinical Outcomes of Vasoplegia in Patients Bridged to Heart Transplantation With Continuous-Flow Left Ventricular Assist Devices

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***Background*—**The presence of a durable left ventricular assist device (LVAD) is associated with increased risk of vasoplegia in the early postoperative period following heart transplantation (HT). However, preoperative predictors of vasoplegia and its impact on survival after HT are unknown. We sought to examine predictors and outcomes of patients who develop vasoplegia after HT following bridging therapy with an LVAD.

***Methods and Results*—**We identified 94 patients who underwent HT after bridging with continuous-flow LVAD from 2008 to 2018 at a single institution. Vasoplegia was defined as persistent low vascular resistance requiring ≥2 intravenous vasopressors within 48 hours after HT for >24 hours to maintain mean arterial pressure >70 mm Hg. Overall, 44 patients (46.8%) developed vasoplegia after HT. Patients with and without vasoplegia had similar preoperative LVAD, echocardiographic, and hemodynamic parameters. Patients with vasoplegia were significantly older; had longer LVAD support, higher preoperative creatinine, longer cardiopulmonary bypass time, and higher Charlson comorbidity index; and more often underwent combined organ transplantation. In a multivariate logistic regression model, older age (odds ratio: 1.08 per year; *P*=0.010), longer LVAD support (odds ratio: 1.06 per month; *P*=0.007), higher creatinine (odds ratio: 3.9 per 1 mg/dL; *P*=0.039), and longer cardiopulmonary bypass time (odds ratio: 1.83 per hour; *P*=0.044) were independent predictors of vasoplegia. After mean follow-up of 4.0 years after HT, vasoplegia was associated with increased risk of all-cause mortality (hazard ratio: 5.20; 95% CI, 1.71–19.28; *P*=0.003).

***Conclusions*—**Older age, longer LVAD support, impaired renal function, and prolonged intraoperative CPB time are independent predictors of vasoplegia in patients undergoing HT after LVAD bridging. Vasoplegia is associated with worse prognosis; therefore, detailed assessment of these predictors can be clinically important. **(*J Am Heart Assoc*. 2019;8:e013108. DOI: 10.1161/JAHA.119.013108.)**

Key Words: heart transplantation • left ventricular assist device • outcome • risk factors • vasoplegia

The use of cardiopulmonary bypass (CPB) can be complicated by severe systemic vasodilation (vasoplegia), a condition characterized by depressed systemic vascular resistance (SVR) and hypotension refractory to administration of vasopressors despite normal or increased cardiac output during and after CPB.[1,2] Vasoplegia occurs in up to 25% of routine cardiac surgeries, and its prevalence is even higher in patients undergoing left ventricular assist device (LVAD) implantation and heart transplantation (HT).[3–5] Several risk factors, including preoperative use of agents such as angiotensin-converting enzyme inhibitors or calcium channel blockers, pre-CPB hemodynamic instability requiring mechanical circulatory support (MCS), and prolonged aortic cross-clamp times, can lead to a systemic inflammatory response, increased production of nitric oxide, and diminished SVR.[6–8]

The utilization of continuous-flow LVADs for stage D heart failure patients as a bridge to transplantation (BTT) is associated with improvement in survival and quality of life.[9–11] However, the postoperative course of LVAD recipients can be challenging because it is often complicated by bleeding, right ventricular failure, arrhythmias, and recurrent infection.[12] In addition, long-term LVAD support may cause endothelial dysfunction resulting in chronic inflammatory activation.[13] These factors may increase the risk of vasoplegia

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Clinical Perspective

What Is New?

- Bridging with left ventricular assist devices is associated with increased risk of vasoplegia syndrome after heart transplantation (HT), but predictors and long-term outcomes of vasoplegia in this population have not been studied.
- This study demonstrates that older age, longer left ventricular assist device support, impaired renal function, and prolonged cardiopulmonary bypass time are independent predictors of vasoplegia in patients undergoing HT after left ventricular assist device support.
- Patients who develop vasoplegia are at significantly increased risk of postoperative complications and long-term all-cause mortality following HT.

What Are the Clinical Implications?

- Vasoplegia is associated with worse prognosis; therefore, detailed assessment of these predictors can be clinically important and help in the evaluation and preparation of patients supported by left ventricular assist devices as a bridge to HT.
- Further research is necessary to examine whether modification of these risk factors for vasoplegia can affect early and long-term outcomes after HT.

following HT for patients with BTT LVADs. Although previous studies have focused on risk factors for vasoplegia following HT or cardiac surgery in general, patients undergoing HT after LVAD bridging represent a unique group who may have a different risk profile and outcomes associated with the development of vasoplegia after HT that have not yet been studied. Furthermore, earlier studies have demonstrated that vasoplegia after HT is associated with increased 30-day mortality and is more common in recipients on pre-HT MCS, in those with higher body mass index, and in those with prolonged CPB and ischemic time.[8,14,15] However, a recent retrospective single-center study of 244 patients after HT (including 56 patients on MCS) found that the presence of vasodilatory shock following HT was associated with increased likelihood of postoperative bleeding and prolonged intubation and hospital stay but had no effect on mortality and graft-rejection rates.[16] Adding to the discrepancy in the literature regarding the impact of vasoplegia on short-term outcomes after HT, the impact on long-term outcomes, particularly in patients bridged with an LVAD before HT, has not been previously investigated.

For the first time, given the increasing numbers and complexity of LVAD recipients listed for HT, we sought to investigate whether there might be unique predictors of vasoplegia after HT that can be related specifically to LVAD bridging and to examine both short- and long-term outcomes among this population. We hypothesized that the development of vasoplegia following HT is common after bridging with an LVAD and that it is associated with increased short- and long-term morbidity and mortality. Consequently, identifying predictors of vasoplegia in this population can be clinically meaningful.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Data Source

Data collection and analysis were performed after Minnesota research authorization was provided by all study participants. Our study protocol was approved by the local institutional review board of the Mayo Clinic College of Medicine. We retrospectively analyzed a cohort of 380 patients receiving an LVAD. Our inclusion criteria included all consecutive adult patients (age ≥18 years) with end-stage heart failure who received axial or centrifugal continuous-flow LVADs (HeartMate II [Thoratec] or HeartWare [HeartWare Inc]) between July 2008 and June 2018 as BTT at the Mayo Clinic in Rochester, Minnesota. Of the 380 patients implanted with an LVAD during the study period, 94 patients underwent HT after bridging therapy with a continuous-flow LVAD and met the inclusion criteria of this study.

Definition

The definition of *vasoplegia* has varied across studies of patients undergoing cardiac surgery.[3,15,17] We defined vasoplegia as persistent low SVR (< 800 dynes/s per cm^5), normal cardiac index (>2.5 L/min per m^2), and normal cardiac function by echocardiogram, requiring ≥2 intravenous vasopressors (eg, vasopressin, norepinephrine, or high-dose epinephrine infusion of >5 μg/min) within 48 hours after HT for >24 hours to maintain mean arterial pressure >70 mm Hg, as described previously by Chan and colleagues[18] and followed by others.[3] All patients were diagnosed with vasoplegia after excluding primary graft dysfunction (PGD) as the cause of their hemodynamic derangement. PGD was determined according to the 2014 International Society for Heart and Lung Transplantation consensus definition,[19] which requires left (PGD-left) or/and right (PGD-right) ventricular graft dysfunction to occur within 24 hours after the completion of the transplantation surgery. An additional grading scale for the severity of LV PGD (mild, moderate, or severe) was determined depending on the level of cardiac dysfunction and the extent of inotrope and

mechanical support required.[19] According to our definition of vasoplegia, which requires the existence of normal cardiac function and cardiac index, there was no overlap between the diagnosis of vasoplegia and PGD in this study.

Clinical and Demographic Data

Demographic, clinical, echocardiographic, hemodynamic, LVAD, and laboratory data were obtained from our prospectively collected clinical database. Medications including renin–angiotensin–aldosterone system antagonists, β-blockers, antiplatelets, vasodilators, antiarrhythmics, and statins were reviewed and recorded at the last visit before HT. Immunosuppressive agents, vasopressors, and inotropes were recorded perioperatively. The estimated glomerular filtration rate was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[20] The prevalence of comorbid conditions, recorded at the last visit before HT, was estimated using the Charlson comorbidity index, as previously described.[21]

Outcomes

The main outcomes of our analysis were all-cause mortality after HT at 30 days and at long-term follow-up. Additional outcomes included length of stay (LOS) in the intensive care unit (ICU), LOS in the hospital, inotrope or vasopressor requirements, duration of mechanical ventilation, and use of extracorporeal membrane oxygenation and intra-aortic balloon pump early after HT. We also evaluated rates of cellular rejection, antibody-mediated rejection, and hemodynamically significant rejection (defined as any biopsy-proven rejection resulting in allograft dysfunction or hemodynamic compromise), as well as renal function, left ventricular ejection fraction, rates of cytomegalovirus and Epstein–Barr viral infection, and cardiac allograft vasculopathy at 1 year after HT. Survival and clinical event information was obtained from subsequent clinic visits and written correspondence from local physicians. Hemodynamic parameters including mean arterial pressure, mean right atrial pressure, mean pulmonary arterial pressure, mean capillary wedge pressure, transpulmonary gradient, cardiac output, cardiac index based on the Fick equation, pulmonary vascular resistance, right ventricular stroke work index, and pulmonary artery pulsatility index ([pulmonary artery systolic pressure minus pulmonary artery diastolic pressure] divided by right arterial pressure) were obtained preoperatively at the time of HT.

Statistical Analysis

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 between those with and without vasoplegia using the χ^2 test for categorical variables (or Fisher exact test if the expected count was <5), ANOVA for normally distributed continuous variables, and the Kruskal–Wallis test for continuous variables with skewed distribution. Univariate and multivariate logistic regression models were constructed to identify factors associated with vasoplegia. A Cox regression model, with adjustment for age, sex, Charlson comorbidity index, combined organ transplantation, and length of LVAD support, was fit to determine the factors associated with the main outcomes of our study. All significance tests were 2-tailed and conducted at the 5% significance level.

Results

Patient Characteristics

Among 380 patients who underwent continuous-flow LVAD implantation during the study period, we identified 94 patients who underwent HT following LVAD bridging. Forty-four (48.9%) HT recipients previously supported with LVAD developed vasoplegia after HT. Pretransplant baseline demographic and clinical characteristics are presented in Table 1. Pretransplant laboratory parameters, medical therapy, and echocardiographic and hemodynamic characteristics are presented in Table 2. Vasoplegic patients were older (56±9 versus 50±11 years; P=0.002), with a longer duration of LVAD support (15.3 versus 10.1 months; P=0.002); had more comorbidities (Charlson comorbidity index 4 versus 3; P=0.001); were more likely to undergo combined organ transplantation (27.3% versus 10%; P=0.03); had higher baseline creatinine (1.5±0.5 versus 1.2±0.4 mg/dL; P<0.001); and had a numerically but not significantly higher prevalence of thyroid disease (17% versus 11%; P=0.08). Most patients in both groups were supported by the HeartMate II LVAD (70.5% among vasoplegic patients, 72% among those without vasoplegia), with the remaining patients supported by the HeartWare LVAD. We did not identify any significant differences in medications (including angiotensin-converting enzyme inhibitors, amiodarone, inotropes) or echocardiographic, LVAD, and hemodynamic parameters between those with and without vasoplegia.

Intraoperative Data

CPB time was longer in vasoplegic patients (195.4±64.1 versus 173.2±43.2 minutes; P=0.049; Table 3) without significant differences in ischemic time (vasoplegia versus no vasoplegia: 190.1±62.4 versus 182.6±57.3 minutes). Most patients in both groups were treated with vasopressin during the surgery (81.8% in vasoplegic versus 72% in nonvasoplegic patients), and there was a numerically but not significantly higher use of norepinephrine intraoperatively in vasoplegic patients (50%

Table 1. Baseline Clinical Characteristics

	All Patients (n=94)	Without Vasoplegia (n=50)	With Vasoplegia (n=44)	*P* Value
Age at transplant, y	52.7±10.8	49.5±11.4	56.4±8.9	0.002
Recipient sex, male	73 (77.7)	38 (76.0)	35 (79.6)	0.681
Race				
White	85 (90.4)	43 (86.0)	42 (95.4)	0.191
Black	6 (6.4)	4 (8.0)	2 (4.6)	
Other	3 (3.2)	3 (6.0)	0 (0.0)	
BMI, kg/m^2	29.3±4.7	29.6±4.8	28.9±4.6	0.506
BSA, m^2	2.1±0.26	2.1±0.26	2.1±0.25	0.772
HF etiology				
ICM	30 (31.9)	17 (34.0)	13 (29.6)	0.644
DCM	45 (47.9)	25 (50.0)	20 (45.5)	0.660
CHD	3 (3.2)	2 (4.0)	1 (2.3)	0.635
Other	16 (17.0)	6 (12.0)	10 (22.7)	0.167
NYHA class				
I–II	32 (34.0)	16 (32.0)	16 (36.4)	0.565
III–IV	62 (66.0)	34 (68.0)	28 (63.6)	
UNOS status				
1A1A	70 (74.5)	36 (72.0)	34 (77.3)	
1B	24 (25.5)	14 (28.0)	10 (22.7)	0.559
Time on LVAD support, mo	13.8 (6.8–23.2)	10.1 (5.3–19.3)	15.3 (10.3–28.8)	0.002
LVAD type				
HeartMate II	67 (71.3)	36 (72.0)	31 (70.5)	0.869
HeartWare	27 (28.7)	14 (28.0)	13 (29.5)	
LVAD speed, rpm				
HeartMate II	9466±370	9399±324	9530±404	0.176
HeartWare	2596±327	2550±292	2646±367	0.456
LVAD flow, L/min				
HeartMate II	5.3±1.1	5.1±1.3	5.5±1.0	0.228
HeartWare	5.4±1.3	5.4±1.6	5.3±1.1	0.921
LVAD power				
HeartMate II	6.5±1.2	6.3±1.5	6.8±1.0	0.118
HeartWare	4.7±1.5	4.9±1.5	4.5±1.5	0.459
LVAD pulse index				
HeartMate II	4.5±1.4	4.7±1.4	4.4±1.4	0.565
HeartWare	3.5±1.8	3.0±1.7	5.0±1.0	0.104
LVAD-associated complications				
Stroke	9 (9.6)	3 (6.0)	6 (13.6)	0.209
Infection	14 (14.9)	5 (10.0)	9 (20.5)	0.155
Pump thrombosis	20 (21.3)	9 (18.0)	11 (25.0)	0.408
RV failure	8 (8.5)	3 (6.0)	5 (11.4)	0.352
GI bleeding	16 (17.0)	8 (16.0)	8 (18.2)	0.779
Mean BP on LVAD	82.8±13.9	81.7±14.8	84.1±12.8	0.417

Continued

Table 1. Continued

	All Patients (n=94)	Without Vasoplegia (n=50)	With Vasoplegia (n=44)	*P* Value
Hypertension	29 (30.9)	16 (32.0)	13 (29.6)	0.797
Hyperlipidemia	36 (38.3)	16 (32.0)	20 (45.5)	0.181
Diabetes mellitus	25 (26.6)	13 (26.0)	12 (27.3)	0.889
Thyroid disease	28 (29.8)	11 (22.0)	17 (38.6)	0.078
COPD	1 (1.1)	0 (0.0)	1 (2.3)	0.284
AF	31 (33.0)	14 (28.0)	17 (38.6)	0.274
Sustained VT	20 (21.3)	9 (18.0)	11 (25.0)	0.408
CCI	4 (2.0–5.0)	3 (2.0–4.0)	4 (3.0–6.0)	0.001
Combined organ transplants	17 (18.1)	5 (10.0)	12 (27.3)	0.030
Heart and kidney	15 (16.0)	4 (8.0)	11 (25.0)	
Heart and liver	2 (2.1)	1 (2.0)	1 (2.3)	
Donor age, y	30.4±10.1	28.9±9.0	32.1±11.2	0.131
Donor sex, male	71 (75.5)	37 (74.0)	34 (77.3)	0.713

Data expressed as mean±SD, median (interquartile range) or n (%). AF indicates atrial fibrillation; BMI indicates body mass index; BP, blood pressure; BSA, body surface area; CCI, Charlson comorbidity index; CHD, congenital heart disease; COPD, chronic obstructive pulmonary disease; DCM, dilated cardiomyopathy; GI, gastrointestinal; HF, heart failure; ICM, ischemic cardiomyopathy; LVAD, left ventricular assist device; NYHA, New York Heart Association; RV, right ventricle; UNOS, United Network for Organ Sharing; VT, ventricular tachycardia.

versus 32%; *P*=0.076; Table 3). Platelet transfusion rates were higher in patients with vasoplegia (17% versus 8%; *P*=0.013), but similar rates of vasoplegic and nonvasoplegic patients received packed red blood cell transfusion (56.8% versus 58%; *P*=0.9).

Predictors of Vasoplegia

Univariate and multivariate regression models were constructed to examine the associations of baseline clinical parameters with vasoplegia after HT (Table 4). Older age (*P*=0.003), longer duration of LVAD support (*P*=0.004), higher creatinine the day before HT (*P*<0.001), combined organ transplantation (*P*=0.036), and higher Charlson comorbidity index (*P*=0.001) were significant predictors of vasoplegia in univariate analysis. Furthermore, we found a marginally significant association between history of hypothyroidism (*P*=0.081) as well as between longer CPB time (*P*=0.061) and the development of vasoplegia (Table 4). In the multivariable regression model, older age (odds ratio: 1.08 per 1-year increase; 95% CI, 1.02–1.14; *P*=0.01), longer duration of LVAD support (odds ratio: 1.06 per 1-month increase; 95% CI, 1.02–1.1; *P*=0.007), higher creatinine on the day before HT (odds ratio: 3.92 per 1 mg/dL increase; 95% CI, 1.07–14.36; *P*=0.039), and longer CPB time (odds ratio: 1.83; 95% CI, 1.02–3.28; *P*=0.044) were independent predictors of vasoplegia (Table 4).

Postoperative Outcomes

Patients with vasoplegia had longer ICU LOS (9.5 versus 6 days; *P*=0.001) and total hospital LOS (19 versus 13.5 days; *P*=0.002; Table 5). Moreover, they required longer duration of vasopressors (5 versus 2 days; *P*<0.001), inotropes (6.0 versus 4.5 days; *P*=0.03), and mechanical ventilation (3.0 versus 1.5 days; *P*<0.001) after HT. We did not identify differences in requirement of intra-aortic balloon pump and extracorporeal membrane oxygenation. There was no difference in 30-day mortality (3% among vasoplegic patients versus 1% among nonvasoplegic patients; *P*=0.25), although the overall number of events was small and underpowered to show significant differences between groups.

Long-Term Outcomes

We found a higher mortality 1 year after HT among vasoplegic patients (16% versus 4%; *P*=0.045). After a mean follow-up of 4 years after HT, all-cause mortality occurred in 28% of patients who developed vasoplegia compared with 6% of patients who did not develop vasoplegia following HT (unadjusted hazard ratio [HR]: 5.2; 95% CI, 1.7–19.3; *P*=0.003; Figure 1). We did not identify differences in risk of acute cellular, antibody-mediated, and hemodynamically significant rejection at 1 year after HT. Furthermore, no differences in allograft function, rates of cytomegalovirus and Epstein-Barr virus infection, and cardiac allograft vasculopathy were observed at 1 year after HT. However, creatinine was significantly higher (1.6±0.6 versus 1.3±0.4 mg/dL; *P*=0.02), and estimated glomerular filtration rate was lower (51 versus 60 mL/min per 1.73 m^2; *P*=0.041) among

Table 2. Pretransplant Laboratory, Treatment, Echocardiographic, and Hemodynamic Data

	All Patients (n=94)	Without Vasoplegia (n=50)	With Vasoplegia (n=44)	*P* Value
Laboratory data				
Hemoglobin, g/dL	11.8±2.1	12.0±2.0	11.5±2.2	0.290
Platelets, k/μL	211.9±78.9	215.6±75.1	207.7±83.7	0.632
Creatinine, mg/dL	1.3±0.45	1.2±0.35	1.5±0.49	<0.001
AST, U/L	36.0 (27.0–46.3)	37.0 (27.0–47.0)	33.0 (26.3–45.8)	0.428
ALT, U/L	28.0 (18.0–43.3)	30.0 (18.0–46.0)	25.0 (18.0–41.8)	0.332
Total bilirubin, mg/dL	0.70 (0.40–1.0)	0.70 (0.48–1.0)	0.70 (0.40–1.0)	0.744
Albumin, g/dL	4.3±0.45	4.3±0.47	4.2±0.42	0.757
TSH, μU/mL	3.0 (1.9–4.6)	3.2 (1.9–5.1)	2.9 (1.9–4.4)	0.898
LDH, U/L	323 (240–437)	330 (251–474)	321 (234–405)	0.171
INR	2.3±0.75	2.2±0.62	2.4±0.88	0.301
NT-proBNP, pg/mL	1239 (626–2856)	932 (509–2987)	1424 (773–2617)	0.396
Treatment				
Aspirin	67 (71.3)	36 (72.0)	31 (70.5)	0.869
ACEI	22 (23.4)	14 (28.0)	8 (18.2)	0.262
ARB	8 (8.5)	4 (8.0)	4 (9.1)	0.850
Digoxin	32 (34.0)	15 (30.0)	17 (38.6)	0.378
β-Blockers	69 (73.4)	35 (70.0)	34 (77.3)	0.426
Aldosterone antagonist	35 (37.2)	18 (36.0)	17 (38.6)	0.792
CCB	19 (20.2)	9 (18.0)	10 (22.7)	0.569
Diuretic	70 (74.5)	37 (74.0)	33 (75.0)	0.912
Hydralazine	8 (8.5)	5 (10.0)	3 (6.8)	0.581
Nitrates	3 (3.2)	2 (4)	1 (2.3)	0.635
Amiodarone	36 (38.3)	17 (34.0)	19 (43.2)	0.361
α-Blockers	6 (6.4)	3 (6.0)	3 (6.8)	0.871
Statins	38 (40.4)	22 (44.0)	16 (36.4)	0.452
Milrinone	15 (16.0)	7 (14.0)	8 (18.2)	0.581
Dobutamine	1 (1.1)	1 (2.0)	0 (0.0)	0.346
Dopamine	2 (2.1)	1 (2.0)	1 (2.3)	0.927
PA pressure-lowering agents	24 (25.5)	13 (26.0)	11 (25.0)	0.912
Echocardiography				
LVEDD, mm	63.6±13.4	63.7±12.9	63.5±14.1	0.928
EF, %	20.6±8.3	21.0±8.0	20.2±8.6	0.659
Interatrial septal position				
Neutral	44 (83.0)	16 (72.8)	28 (90.3)	0.220
Right shift	4 (7.6)	3 (13.6)	1 (3.2)	
Left shift	5 (9.4)	3 (13.6)	2 (6.5)	
Interventricular septal position				
Neutral	45 (86.6)	16 (84.2)	29 (87.9)	0.904
Right shift	5 (9.6)	2 (10.5)	3 (9.1)	
Left shift	2 (3.8)	1 (5.3)	1 (3.0)	

Continued

Table 2. Continued

	All Patients (n=94)	Without Vasoplegia (n=50)	With Vasoplegia (n=44)	*P* Value
RV enlargement				
Normal	9 (9.6)	5 (10.0)	4 (9.1)	0.494
Mild, mild-moderate	31 (33.0)	13 (26.0)	18 (40.9)	
Moderate, moderate-severe	44 (46.8)	26 (52.0)	18 (40.9)	
Severe	10 (10.6)	6 (12.0)	4 (9.1)	
RV systolic function				
Normal	5 (5.3)	2 (4.0)	3 (6.8)	0.691
Mild, mild-moderate	20 (21.3)	9 (18.0)	11 (25.0)	
Moderate, moderate-severe	58 (61.7)	32 (64.0)	26 (59.1)	
Severe	11 (11.7)	7 (14.0)	4 (9.1)	
RVSP	32.1±8.9	31.0±8.9	32.1±8.9	0.282
AV opening				
Every cycle	19 (20.2)	9 (18.0)	10 (22.7)	0.659
Intermittent	17 (18.1)	8 (16.0)	9 (20.5)	
Closed	58 (61.7)	33 (66.0)	25 (56.8)	
AI severity				
Normal	48 (51.1)	28 (56.0)	20 (45.5)	0.398
Mild, mild-moderate	38 (40.4)	19 (38.0)	19 (43.2)	
Moderate, moderate-severe	6 (6.4)	3 (6.0)	3 (6.8)	
Severe	2 (2.1)	0 (0.0)	2 (4.5)	
MR severity				
Normal	22 (23.4)	13 (26.0)	9 (20.5)	0.363
Mild, mild-moderate	53 (56.4)	27 (54.0)	26 (59.1)	
Moderate, moderate-severe	11 (11.7)	4 (8.0)	7 (15.9)	
Severe	8 (8.5)	6 (12.0)	2 (4.5)	
TR severity				
Normal	23 (24.5)	12 (24.0)	11 (25.0)	0.275
Mild, mild-moderate	46 (48.9)	22 (44.0)	24 (54.5)	
Moderate, moderate-severe	16 (17.0)	12 (24.0)	4 (9.1)	
Severe	9 (9.6)	4 (8.0)	5 (11.4)	
Inflow cannula velocity, m/s	0.9 (0.6–1.0)	0.95 (0.6–1.0)	0.9 (0.65–1.0)	0.914
Outflow cannula velocity, m/s	1.0 (1.0–1.4)	1.1 (0.93–1.3)	1.0 (1.0–1.7)	0.755
Invasive hemodynamics				
Heart rate, bpm	80.8±16.7	79.5±13.1	81.7±18.6	0.656
RAP, mm Hg	12.3±6.6	11.9±6.0	12.5±7.0	0.742
PCWP, mm Hg	13.8±7.8	13.3±7.5	14.0±8.1	0.748
mPAP, mm Hg	25.8±9.3	25.1±7.7	26.3±10.2	0.652
TPG, mm Hg	12.2±5.1	12.0±4.3	12.3±5.6	0.870
DPG, mm Hg	3.6±4.3	2.6±3.8	4.2±4.5	0.215
PVR, WU	2.5±1.3	2.5±1.3	2.5±1.3	0.901
CO, L/min	5.0±1.1	4.8±0.86	5.0±1.2	0.464

Continued

Table 2. Continued

	All Patients (n=94)	Without Vasoplegia (n=50)	With Vasoplegia (n=44)	*P* Value
Cardiac index, L/min/m^2	2.4±0.63	2.4±0.76	2.4±0.56	0.904
RVSWI, g×m/m^2	5.6±4.0	6.2±3.6	5.3±4.2	0.441
PAPi	2.7±3.0	2.5±1.9	2.8±3.6	0.706

Data expressed as mean±SD, median (interquartile range), or n (%). ACEI indicates angiotensin-converting enzyme inhibitor; AI denotes aortic insufficiency; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; AV, aortic valve; CCB, calcium channel blocker; CO, cardiac output; DPG, diastolic pulmonary gradient; EF, ejection fraction; INR, international normalized ratio; LDH, lactate dehydrogenase; LVEDD, left ventricular end-diastolic diameter; mPAP, mean pulmonary artery pressure; MR, mitral regurgitation; NT-proBNP, N-terminal pro–brain natriuretic peptide; PA, pulmonary artery; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricle; RVSP, right ventricular systolic pressure; RVSWI, right ventricular stroke work index; TPG, transpulmonary pressure gradient; TR, tricuspid regurgitation; TSH, thyroid-stimulating hormone; WU, Wood units.

patients with vasoplegia at 1 year of follow-up. Cox regression analysis, with adjustment for recipient age, sex, Charlson comorbidity index, combined organ transplantation, and length of LVAD support, identified vasoplegia as an independent predictor of long-term mortality (adjusted HR: 4.1; 95% CI, 1.2–14.5; *P*=0.020) after a mean follow-up time of 4 years after HT.

An additional analysis including 90 patients who survived at least 30 days following HT (after excluding the 3 deaths in the vasoplegia group and 1 death in the nonvasoplegia group within the first 30 days after HT) showed that patients with vasoplegia had significantly lower cumulative survival rates compared with patients who did not develop vasoplegia (*P*=0.005; Figure 2A). Among the survivors at 30 days, patients with vasoplegia experienced a large increased risk of death compared with patients without vasoplegia (unadjusted HR: 5.9; 95% CI, 1.5–23.0; *P*=0.011). After adjustment for age, sex, Charlson comorbidity index, combined organ transplantation, and length of LVAD support, vasoplegia remained an independent predictor of all-cause mortality in this cohort (adjusted HR: 4.6; 95% CI, 1.1–20.1; *P*=0.040). Furthermore, 80 patients continued follow-up >1 year after HT (after excluding 7 and 2 deaths in the vasoplegia and nonvasoplegia groups, respectively, in addition to 5 patients with <1-year follow-up after HT). When the survival analysis was restricted to this group of patients, longer term analysis showed significantly lower cumulative survival rates in the vasoplegic group (*P*=0.02; Figure 2B). In the unadjusted Cox regression analysis of this smaller group, patients with vasoplegia had increased risk of all-cause mortality compared with those without vasoplegia (HR: 6.1; 95% CI, 1.1–34.9; *P*=0.041), but this association was no longer significant after adjustment for age, sex, Charlson comorbidity index, combined organ transplantation, and length of LVAD support (HR: 5.3; 95% CI, 0.76–36.7; *P*=0.091).

Discussion

This retrospective single-center study demonstrates the following salient findings: (1) approximately half of the patients bridged with LVAD before HT developed vasoplegia following HT; (2) vasoplegic patients were significantly older

Table 3. Intraoperative Data

	All Patients (n=94)	Without Vasoplegia (n=50)	With Vasoplegia (n=44)	*P* Value
Bypass time, min	183.6±54.8	173.2±43.2	195.4±64.1	0.049
Ischemic time, min	185.9±59.3	182.6±57.3	190.1±62.4	0.576
Vasopressor use*				
Norepinephrine	38 (40.4)	16 (32.0)	22 (50.0)	0.076
Phenylephrine	6 (6.4)	3 (6.0)	3 (6.8)	0.871
Vasopressin	72 (76.6)	36 (72.0)	36 (81.8)	0.262
Epinephrine	76 (80.9)	40 (80.0)	36 (81.8)	0.823
PRBC transfusion	54 (57.4)	29 (58.0)	25 (56.8)	0.908
FFP transfusion	33 (35.1)	16 (32.0)	17 (38.6)	0.501
Platelet transfusion	25 (26.6)	8 (16.0)	17 (38.6)	0.013

Data expressed as mean±SD, median (interquartile range), or n (%). FFP indicates fresh frozen plasma; PRBC, packed red blood cell.
*Vasopressor use represents only the intraoperative use of these vasopressors and not necessarily use during recovery time in the intensive care unit postoperatively.

Table 4. Univariate and Multivariate Predictors of Vasoplegia After HT Among Patients Bridged With LVAD

Predictor	OR (95% CI)	*P* Value
Univariate model		
Age (per 1-y increase)	1.07 (1.02–1.12)	0.003
Length of LVAD support (per 1-mo increase)	1.06 (1.02–1.10)	0.004
History of hypothyroidism	2.23 (0.90–5.51)	0.081
CCI	1.54 (1.19–1.99)	0.001
Combined organ transplantation	3.37 (1.08–10.53)	0.036
Creatinine day prior (per 1-mg/dL increase)	7.72 (2.30–25.87)	<0.001
CPB time (per 1-h increase)	1.68 (0.98–2.89)	0.061
Multivariate model*		
Age (per 1-y increase)	1.08 (1.02–1.14)	0.010
Length of LVAD support (per 1-mo increase)	1.06 (1.02–1.10)	0.007
Creatinine day prior (per 1-mg/dL increase)	3.92 (1.07–14.36)	0.039
CPB time (per 1-h increase)	1.83 (1.02–3.28)	0.044

CCI indicates Charlson comorbidity index; CPB, cardiopulmonary bypass; HT, heart transplantation; LVAD, left ventricular assist device; OR, odds ratio.
*$P<0.0001$ for the whole model; $R^2=27\%$; $df=4$; $\chi^2=34.2$.

and had longer LVAD support time, higher preoperative creatinine, longer CPB time, more comorbidities, and higher rates of combined organ transplantation; (3) older age, longer LVAD support, pre-HT renal function, and CPB time were independent predictors of vasoplegia; (4) vasoplegic patients had longer ICU LOS, and required longer duration of vasopressors and mechanical ventilatory support; and (5) patients who developed vasoplegia following HT were at significantly increased risk of long-term mortality compared with patients without vasoplegia.

Previous studies have focused on predictors of vasoplegia after HT in the general HT population, and, to the best of our knowledge, this study is the first to specifically address the question of whether there might be unique predictors of vasoplegia among patients supported by an LVAD as a bridge to HT. We limited our analysis to the LVAD population because patients supported by continuous-flow LVAD before HT represent a unique and growing cohort of patients with potentially different underlying mechanisms for the development of post-HT vasoplegia. This difference is due to the continuous-flow circulation physiology associated with the LVAD function, which may persistently affect post-HT vasomotor activity even after LVAD explantation. Moreover, LVAD patients may develop LVAD-related complications, including stroke, chronic infection, and pump dysfunction, that may have chronic systemic consequences and thus increase the risk of vasoplegia after HT. In this setting, we hypothesized that a unique set of predictors of vasoplegia (eg, LVAD parameters, LVAD-related complications, and the length of LVAD support) may exist in comparison with the previously tested predictors in the general HT population, which is more heterogeneous (eg, patients on chronic inotropes and others on temporary MCS devices). Given the growing number of patients undergoing HT after LVAD support and the decreased long-term survival of patients with post-HT vasoplegia, detailed assessment of the preoperative risk factors of vasoplegia found in our study is clinically important. First, we confirmed that previously reported risk factors for vasoplegia in the general HT population, including advanced age and prolonged CPB time, are still associated with increased risk of vasoplegia after LVAD bridging; therefore, they are not unique to the LVAD population. Second, we found that the length of LVAD support was a significant predictor of post-HT vasoplegia, independent of other risk factors including reoperative status, CPB time, and combined organ transplantation, supporting specific LVAD-driven factors contributing to the development of vasoplegia syndrome. Consequently, the duration of LVAD support is an important factor that should be considered in the evaluation and preparation of patients supported by LVADs for HT. Based on our results, other LVAD-related parameters and complications were not found to be significantly associated with vasoplegia after HT, but larger studies are necessary to confirm these findings.

Our study is the first to examine the long-term outcomes associated with vasoplegia >1 year following HT and the first of its kind to exclusively examine predictors of vasoplegia after HT among patients who underwent preceding bridging therapy with an LVAD. Previous studies have conflicting results regarding the impact of vasoplegia on postoperative outcomes during a short period of follow-up, with some

Table 5. Post-HT Outcomes

	All Patients (n=94)	Without Vasoplegia (n=50)	With Vasoplegia (n=44)	*P* Value
ICU stay, d	7.0 (5.0–12.0)	6.0 (5.0–8.0)	9.5 (6.0–16.0)	0.001
On vasopressors, d	3.5 (2.0–6.0)	2.0 (2.0–4.0)	5.0 (3.0–9.0)	<0.0001
On inotropes, d	5.0 (3.0–8.0)	4.5 (3.0–7.0)	6.0 (4.0–9.0)	0.032
Intubated, d	2.0 (1.0–4.0)	1.5 (1.0–2.3)	3.0 (2.0–6.0)	0.001
Total hospital stay, d	16.0 (11.0–25.0)	13.5 (10.0–20.0)	19.0 (15.0–31.5)	0.002
ECMO use	7 (7.4)	4 (8.0)	3 (6.8)	1.000
IABP use	7 (7.4)	4 (8.0)	3 (6.8)	1.000
30-d mortality	4 (4.3)	1 (2.0)	3 (6.8)	0.237
1-y mortality	9 (9.6)	2 (4.0)	7 (15.9)	0.045
Last follow-up mortality	15 (16.0)	4 (8.0)	11 (25.0)	0.003
1-y treated ACR	9 (9.6)	5 (10.0)	4 (9.1)	1.000
1-y treated AMR	10 (10.6)	3 (6.0)	7 (15.9)	0.181
1-y treated ACR or AMR	18 (19.1)	8 (16.0)	10 (22.7)	0.408
1-y HSR*	4 (4.3)	4 (8.0)	0 (0.0)	0.120
1-y creatinine, mg/dL	1.4±0.51	1.3±0.36	1.6±0.64	0.020
1-y eGFR, mL/min	55.0 (42.8–71.3)	60.0 (46.0–76.3)	51.0 (39.0–67.3)	0.041
1-y allograft LVEF, %	61.7±6.9	62.0±8.1	61.3±5.0	0.640
1-y CMV infection	18 (19.1)	13 (26.0)	5 (11.4)	0.072
1-y EBV infection	3 (3.2)	1 (2.0)	2 (4.6)	0.598
1-y ISHLT CAV grade				
Grade 0	78 (83.9)	42 (84.0)	36 (83.7)	0.971
Grade 1	15 (16.1)	8 (16.0)	7 (16.3)	

Data expressed as mean±SD, median (interquartile range), or n (%). Fisher exact test was used if expected count was <5. ACR indicates allograft cellular rejection; AMR, antibody-mediated rejection; CAV, cardiac allograft vasculopathy; CMV, cytomegalovirus; EBV, Epstein–Barr virus; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HSR, hemodynamically significant rejection; HT, heart transplantation; IABP, intra-aortic balloon bump; ICU, intensive care unit; ISHLT, International Society of Heart and Lung Transplantation; LVEF, left ventricular ejection fraction.

*HSR was defined as any cellular or antibody-mediated graft rejection resulting in significant allograft dysfunction or hemodynamic instability.

studies finding no association with all-cause mortality[16,18] and others showing increased 30-day[15,22] and 1-year[3] mortality. In this study, we found vasoplegia to be associated with worse long-term survival, which could not be attributed to allograft dysfunction, rejection, or cardiac allograft vasculopathy during the first year after HT. A plausible explanation for this phenomenon is that prolonged ICU stay, total hospital stay, and mechanical ventilation leads to delayed recovery, higher risk of nosocomial infections, malnutrition, worse renal function, and other noncardiac complications that adversely affect long-term survival. Furthermore, it is possible that vasoplegic patients are generally sicker, with a higher burden of comorbidities not necessarily captured by our retrospective analysis, and these factors may subsequently result in worse long-term outcomes.

Although LVAD implantation as BTT leads to hemodynamic stabilization and improvement in functional status and survival, it does not seem to obviate the risk of vasoplegia after HT, particularly in older HT recipients with renal dysfunction and prolonged LVAD support and CPB time. In fact, utilization of MCS devices (including LVAD) appears to increase the risk of vasoplegia following HT, as suggested by other studies.[15,18,22] Although limited by the small number of patients undergoing HT after bridging with mechanical support devices and the lack of information about the time these patients were supported by these devices, Patarroyo et al[15] have shown that ≈30% of patients supported by mechanical devices (most of which were LVADs) developed vasoplegia after HT compared with only 7% of those who were not supported by such devices. However, other studies involving patients supported by nonpulsatile LVADs presented varying rates of vasoplegia ranging from 20%[22] to 45%[18] depending on the definition and severity of vasoplegia used in these studies. Our findings indicate a notably higher incidence of post-HT vasoplegia among patients bridged with an LVAD than was reported in other studies and that may be explained by greater comorbidities and increased frequency of combined organ transplantation in our cohort, thus prolonging the

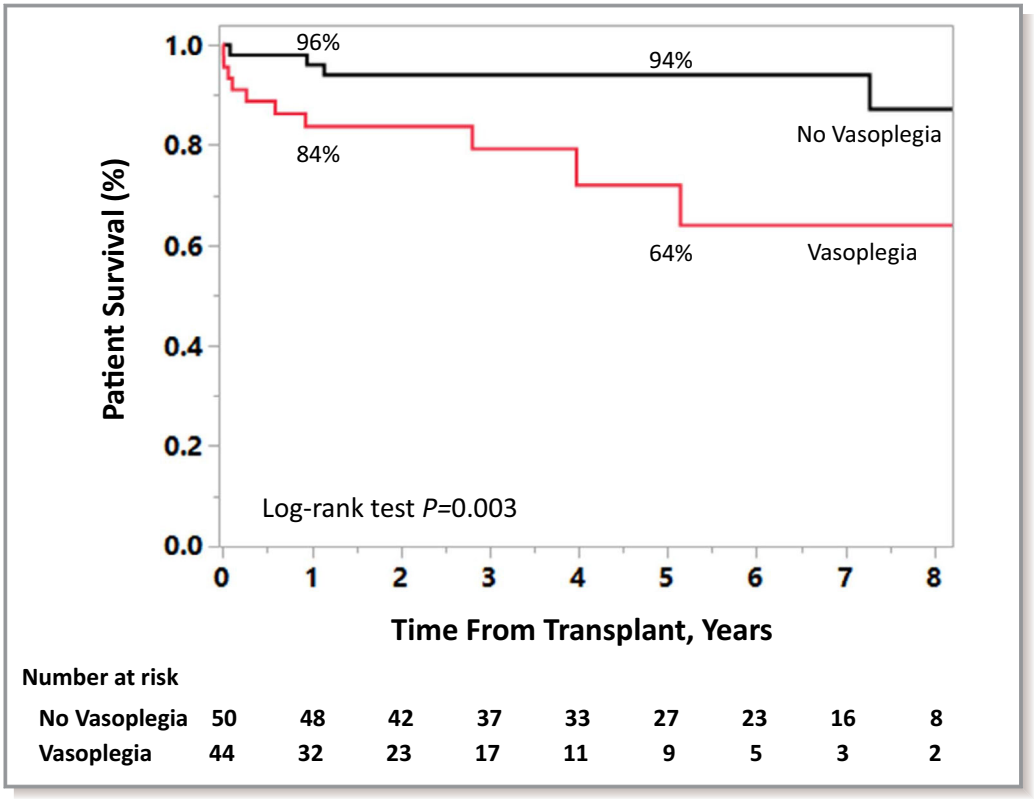

Figure 1. Kaplan–Meier estimates of survival after heart transplantation (HT) among patients bridged with a left ventricular assist device, comparing patients with and without vasoplegia after HT (P=0.003 by log-rank test). Survival rates in the nonvasoplegic vs vasoplegic groups, respectively, were 96% (95% CI, 93.2–98.8%) vs 84% (95% CI, 78.4–89.6%) at 1 year and 94% (95% CI, 90.6–97.4%) vs 64% (95% CI, 52.8–75.2%) at 5 years.

waiting time for HT while on LVAD support and increasing CPB time during transplantation.

Patients with and without vasoplegia following HT had similar 30-day mortality rates. This finding can be explained by better LVAD and HT candidate selection; hemodynamic stabilization of critically ill patients with temporary and permanent MCS; improved postoperative course and survival with continuous-flow LVADs compared with pulsatile devices; and, most important, earlier recognition and more effective management of vasoplegia after HT. Consistent with our observation, a retrospective single-center study involving 240 HT recipients has shown that vasoplegia was associated with longer ICU stay but similar short-term mortality in patients without PGD.[23] Because PGD and vasoplegia share common risk factors and pathogenic mechanisms, the occurrence of both conditions in some HT recipients portends adverse short outcomes. In the absence of PGD, the effects of vasoplegia on in-hospital outcomes may be less deleterious.[23] However, prolonged intubation and increased requirements for administration of intravascular volume can adversely affect right ventricular function, worsen renal function, and prolong hospital stay of vasoplegic patients. Despite these explanations, because early splitting of the Kaplan–Meier curves was noted between vasoplegic and nonvasoplegic patients, it is likely that we were underpowered to find significant differences in mortality between groups given the small number of events that occurred during the first 30 days after HT. Consequently, adequately powered multicenter studies are needed to evaluate differences in short-term mortality risk in association with development of vasoplegia following HT.

Accumulating evidence from prospective randomized blinded clinical trials and a meta-analysis of these trials suggests that administration of vasopressin or a combination of vasopressin with catecholamines is associated with lower rates of atrial fibrillation[24,25] and, in some studies, mortality[24] compared with administration of norepinephrine alone. In refractory vasoplegia cases, a single dose of intravenous methylene blue can improve SVR by reducing vascular response to nitric oxide.[26] However, its efficacy has not been validated in prospective randomized clinical trials. Adoption of minimally invasive surgical techniques (eg, left thoracotomy) may decrease incidence of right ventricular failure after LVAD implantation,[27] and the use of minimally invasive techniques

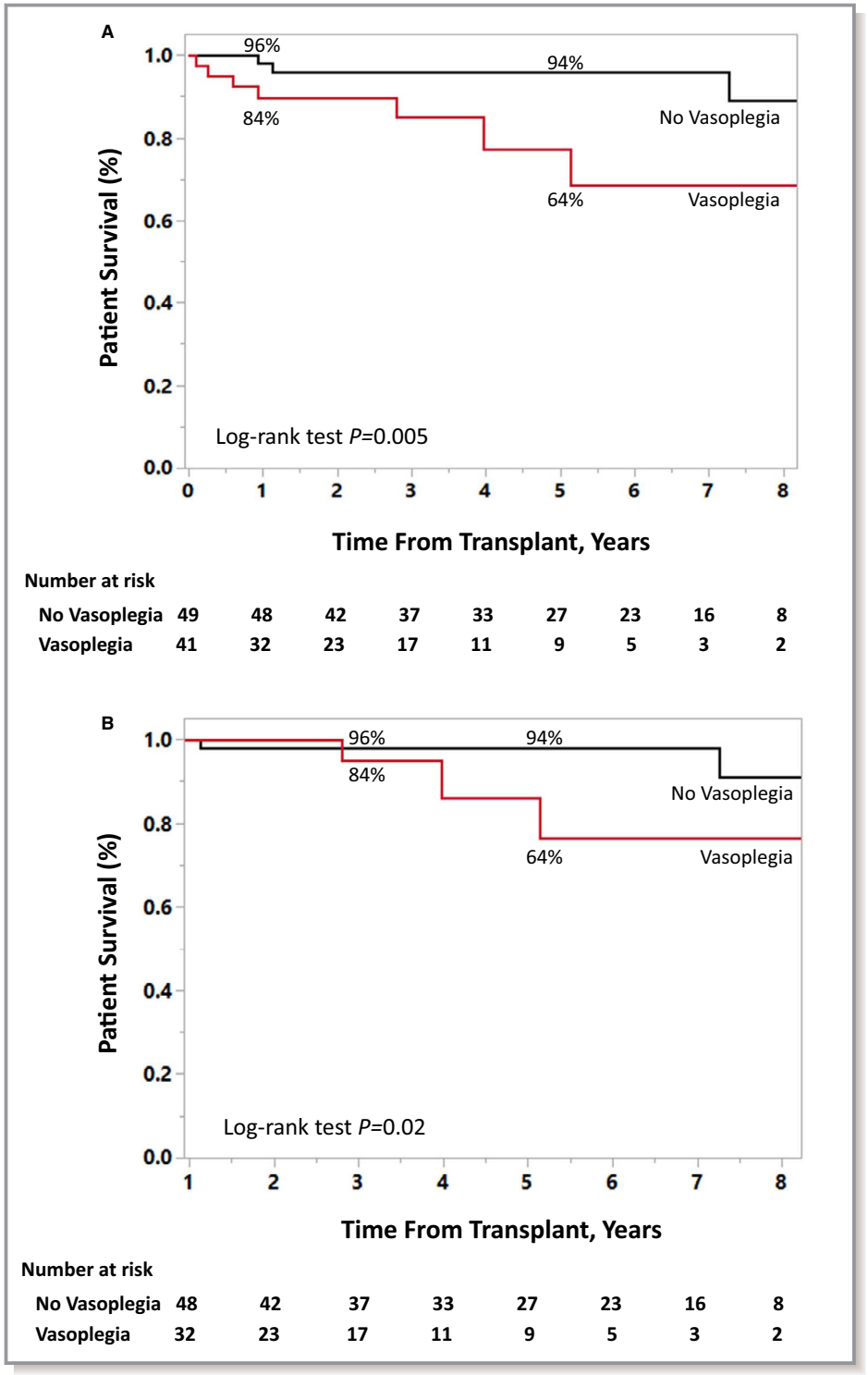

Figure 2. Kaplan–Meier estimates of survival at 30 days (**A**) and 1 year (**B**) comparing patients with and without vasoplegia after heart transplantation. Among those who survived 30 days, survival rates in the nonvasoplegic vs vasoplegic groups, respectively, were 98% (95% CI, 96.1–99.9%) vs 90% (95% CI, 85.1–94.9%) at 1 year and 96% (95% CI, 93.1–98.9%) vs 69% (95% CI, 57.3–80.7%) at 5 years (P=0.005). Among those who survived to 1 year, survival rates in the nonvasoplegic vs vasoplegic groups, respectively, were 98% (95% CI, 96.0–100.0%) vs 95% (95% CI, 90.2–99.8%) at 3 years and 98% (95% CI, 96.0–100.0%) vs 77% (95% CI, 74.7–89.3%) at 5 years (P=0.020).

in BTT LVAD patients may decrease CPB time, bleeding, and blood-product requirement after sternotomy for HT. Other strategies to restore vascular function in refractory cases include corticosteroids, angiotensin II, vitamin B12, and prothrombin complex concentrate,[4] but their effects on perioperative outcomes have not been well studied.

Despite the advances in recognition and treatment of vasoplegia, the incidence of this morbidity remains high, particularly among patients who undergo LVAD implantation or HT. Moreover, the pathophysiology behind vasoplegia is complex and multifactorial, including increased activation of proinflammatory cytokines, vasodilatory peptides, and resistance to catecholamine-based vasopressors.[28] Patients with advanced heart failure listed for HT are already in a chronic inflammatory state. In the setting of prior LVAD support, redo sternotomy typically results in longer CPB due to explantation of the LVAD, higher perioperative bleeding risk and blood-product requirement, more pronounced inflammatory state, and subsequent release of vasoactive mediators.[15] Furthermore, among LVAD recipients with preexisting renal dysfunction, diminished clearance of various circulating vasodilators may further exacerbate this phenomenon. LVAD patients are also frequently treated with angiotensin-converting enzyme inhibitors, heparin, and amiodarone, which have been identified as risk factors for vasoplegia in previous studies,[1] although they were not confirmed as significant determinants of vasoplegia in our study. The presence of additional risk factors encountered in patients supported with LVAD may lead to marked reduction in SVR and may explain the higher incidence of vasoplegia among these patients after HT. Indeed, LVAD has been proposed in previous retrospective single-center studies to be an independent risk factor for vasoplegia.[15,22] Our study further extends these findings by showing that longer LVAD support is associated with increased risk of vasoplegia among HT recipients. Whether LVAD support itself promotes greater chronic inflammation that is accentuated by longer support, thus inducing postoperative vasoplegia, is unknown. Studies have shown that continuous-flow LVADs affect normal vasomotor activity through changes in nitric oxide synthesis and release.[29] Furthermore, LVAD support results in increased wall thickness, collagen, and smooth muscle content accompanied by a reduction in elastin of the aortic wall.[30] However, whether long-term continuous flow alters vascular response and disturbs the autoregulatory vasoresponsiveness of blood vessels after subsequent cardiac surgery warrants further investigation.

Limitations of our study should be acknowledged. This study is retrospective, representative of a single-center experience and practice. Another limitation of this study is that some relevant clinical variables might not reach significance because of a small sample size rather than having a neutral effect on vasoplegia outcome. The high prevalence of combined organ transplantation in our program may limit generalizability of our findings to other transplant centers that perform single HT only. Moreover, no patients with HeartMate 3 devices met the inclusion criteria. Consequently, our results might not be generalized to all LVAD centers and populations. Despite these limitations, the main strength of our study is the inclusion of HT recipients who were previously supported by LVADs and the long-term follow-up.

In conclusion, vasoplegia is a common perioperative complication of HT among LVAD recipients. Despite successful transplantation, vasoplegia affects not only short-term outcomes such as ICU, hospital stay, and duration of mechanical ventilation but also long-term survival following HT. Age, length of LVAD support, preoperative renal function, and CPB time are independent predictors of vasoplegia. Further research is warranted to examine whether modification of these risk factors for vasoplegia can affect early and long-term outcomes after HT.

Disclosures

None.

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