

ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

Predictors and Impact of Prolonged Vasoplegia After Continuous-Flow Left Ventricular Assist Device Implantation



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ABSTRACT

BACKGROUND Vasoplegia after cardiac surgery is associated with adverse outcomes. However, the clinical effects of vasoplegia and the significance of its duration after continuous-flow left ventricular assist device (CF-LVAD) implantation are less known.

OBJECTIVES This study aimed to identify predictors of and outcomes from transient vs prolonged vasoplegia after CF-LVAD implantation.

METHODS The study was a retrospective review of consecutive patients who underwent CF-LVAD implantation between January 1, 2005, and December 31, 2017. Vasoplegia was defined as the presence of all of the following: mean arterial pressure ≤ 65 mm Hg, vasopressor (epinephrine, norepinephrine, vasopressin, or dopamine) use for >6 hours within the first 24 hours postoperatively, cardiac index ≥ 2.2 L/min/m² and systemic vascular resistance <800 dyne/s/cm⁵, and vasodilatory shock not attributable to other causes. Prolonged vasoplegia was defined as that lasting 12 to 24 hours; transient vasoplegia was that lasting 6 to <12 hours. Patient characteristics, outcomes, and risk factors were analyzed.

RESULTS Of the 600 patients who underwent CF-LVAD implantation during the study period, 182 (30.3%) developed vasoplegia. Mean patient age was similar between the vasoplegia and no-vasoplegia groups. Prolonged vasoplegia (n = 78; 13.0%), compared with transient vasoplegia (n = 104; 17.3%), was associated with greater 30-day mortality (16.7% vs 5.8%; $P = 0.02$). Risk factors for prolonged vasoplegia included preoperative dialysis and elevated body mass index.

CONCLUSIONS Compared with vasoplegia overall, prolonged vasoplegia was associated with worse survival after CF-LVAD implantation. Treatment to avoid or minimize progression to prolonged vasoplegia may be warranted. (JACC Adv 2024;3:100916) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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**ABBREVIATIONS
AND ACRONYMS****ACEI** = angiotensin-converting enzyme inhibitor**AKI** = acute kidney injury**ARB** = angiotensin receptor blocker**CF-LVAD** = continuous-flow left ventricular assist device**CVP** = central venous pressure**IL** = interleukin**INTERMACS** = Interagency Registry for Mechanically Assisted Circulatory Support**MAP** = mean arterial pressure**MCS** = mechanical circulatory support**MELD** = Model for End-Stage Liver Disease**RVF** = right ventricular failure**SVR** = systemic vascular resistance

Vasoplegia (vasoplegic shock) is characterized by high cardiac output with low systemic vascular resistance (SVR), resulting in refractory hypotension. Thought to arise as a severe systemic inflammatory response, vasoplegia is most frequently encountered in patients with sepsis, but it is also common after cardiac surgery and cardiopulmonary bypass. Depending on how vasoplegia is defined, its reported incidence ranges from 5% to nearly 50% among patients undergoing heart transplant,¹⁻⁶ general cardiac surgery,⁷⁻⁹ or left ventricular assist device implantation.^{2,4,10} These studies consistently associate vasoplegia with poor outcomes, especially early morbidity and death.¹⁻⁹ Nonetheless, little consensus exists on an appropriate definition of vasoplegia, and the literature is widely heterogeneous regarding risk factors and treatment strategies for vasoplegia in patients undergoing

continuous-flow left ventricular assist device (CF-LVAD) implantation (Supplemental Table 1).^{2,4,10}

We conducted a study to characterize vasoplegia in the CF-LVAD population, investigate the impact of vasoplegia on postoperative outcomes, and identify predictors of vasoplegia development. Objective definitions of postoperative vasoplegia were used to more accurately identify the patient cohort. Also, we characterized the duration of vasoplegia by identifying patients with transient vasoplegia and prolonged vasoplegia. We hypothesized that patients who developed vasoplegia, especially prolonged vasoplegia, after CF-LVAD implantation would have more adverse outcomes and poorer survival.

METHODS

Data were retrospectively reviewed from consecutive adults (age ≥ 18 years) who underwent primary CF-LVAD implantation at our institution between January 1, 2005, and December 31, 2017. The study was approved by the Baylor College of Medicine Institutional Review Board.

Baseline patient characteristics were collected from clinical records, as were hourly hemodynamic

data and vasopressor use during the first postoperative 24 hours. Patients who received multiple forms of temporary mechanical circulatory support (MCS) in the index admission before CF-LVAD implantation were counted for each type of MCS, but only once to calculate overall MCS use. With this approach, the sum of the individual MCS devices exceeds the total MCS use.

Postoperative complications were determined by chart review and included early hospital readmission (within 30 days of discharge from index admission), right ventricular failure (RVF), acute kidney injury (AKI), neurological dysfunction, and infection. Perioperative (within 30 days of CF-LVAD implantation) stroke was identified from the presence of symptoms, results from cerebral computed tomography imaging, and confirmatory neurology consultation. Postoperative acute renal failure was defined as a 3-fold increase in creatinine level from baseline or need for postoperative renal replacement therapy during the index admission.

Postoperative vasoplegia was defined as a severe hypotensive state characterized by: 1) mean arterial pressure (MAP) ≤ 65 mm Hg; 2) treatment with a vasopressor (epinephrine, norepinephrine, vasopressin, or dopamine) for >6 hours within the first 24 hours postoperatively; 3) cardiac index ≥ 2.2 L/min/m² (calculated from measurements obtained with an indwelling pulmonary artery catheter) and SVR < 800 dyne/s/cm²; and 4) vasodilatory shock not attributable to infection, cardiogenic shock, RVF, or any other cause. Patients taking milrinone regularly were not classified as having vasoplegia.

In accordance with Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) descriptions,¹¹ we defined RVF as prolonged signs and symptoms of RV dysfunction: central venous pressure (CVP) > 18 mm Hg with a cardiac index < 2.0 L/min/m² in the absence of increased left atrial filling pressure or pulmonary capillary wedge pressure > 18 mm Hg, cardiac tamponade, ventricular arrhythmias, and/or pneumothorax requiring either right VAD implantation or inhaled nitric oxide or inotropic therapy for ≥ 14 days after CF-LVAD implantation.

To avoid the confounding effect of postoperative epinephrine use on the dosage of other vasopressors,

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we categorized preoperative epinephrine as an inotrope and postoperative epinephrine as a vasopressor, reflecting our institutional practice pattern. Usage and dosage of specific vasopressors was determined by the treating clinicians. Our general hemodynamic targets are a MAP of approximately 80 mm Hg and a CVP of around 10 mm Hg, consistent with recommendations from the International Society for Heart and Lung Transplantation.¹²

When indicated, renal replacement therapy was used with continuous venovenous hemodialysis with an effluent flow rate of 25 mL/kg/h and a blood flow rate of 200 to 300 mL/min.¹³ Clinical decision-making was multispecialty, with daily rounding by a comprehensive team that included cardiovascular surgeons, heart failure cardiologists, critical care specialists, and pharmacists.

The definitions of vasoplegia in previous studies and the current study are listed in [Supplemental Table 1](#) for comparison. Postoperative vasoplegia was further classified as transient or prolonged. Our focus on vasoplegia was limited to the first 24 hours postoperatively; thus, we defined transient vasoplegia as lasting 6 to <12 hours and prolonged vasoplegia as lasting 12 to 24 hours.

Primary end points were development of postoperative vasoplegia and development of prolonged vasoplegia. Secondary end points included postoperative adverse outcomes, hospital length of stay, early readmission, and survival. Patients were followed until transplant, death, or the end of the observation period.

STATISTICAL ANALYSIS. Categorical variables are shown as number and percentage and compared by using the Pearson chi-square test or Fisher exact test, as appropriate. Continuous variables are described as mean ± SD and compared by using unpaired *t*-tests (for normally distributed data) or Wilcoxon rank sum tests (for non-normally distributed data).

Risk factor models were developed for binary outcome variables, including postoperative and prolonged vasoplegia. The covariates in each model included known risk factors ([Supplemental Table 1](#)) that were available in our data set as well as additional variables that were selected from all available patient characteristics (age, sex, comorbidities, laboratory values, hemodynamic values, and medication history) by performing a modified Poisson analysis with robust selection. For each binary response and the covariates, a modified Poisson regression analysis with robust standard errors^{14,15} was performed to identify risk factors and estimate relative risk (RR).

TABLE 1 Baseline Characteristics of Patients Who Developed Postoperative Vasoplegia Compared With Patients Who Did Not

	Vasoplegia (n = 182)	No Vasoplegia (n = 418)	P Value
Demographic data			
Male	163 (89.6)	313 (74.9)	<0.001
Age, y	53.8 ± 13.0	55.2 ± 13.5	0.20
BMI, kg/m ²	31.7 ± 20.4	27.7 ± 6.4	0.01
Ischemic cardiomyopathy	82 (45.1)	197 (47.1)	0.60
Bridge to transplant	91 (50.0)	227 (54.3)	0.60
Past medical history			
Diabetes mellitus	81 (44.5)	183 (43.8)	0.90
Hypertension	118 (64.8)	257 (61.5)	0.40
COPD	24 (13.2)	63 (15.1)	0.50
Stroke	37 (20.3)	54 (12.9)	0.047
Dialysis	16 (8.8)	18 (4.3)	0.03
Previous cardiac surgery	68 (37.4)	143 (34.2)	0.50
Previous mechanical circulatory support	80 (44.0)	188 (45.0)	0.60
Intra-aortic balloon pump	70 (38.5)	160 (38.3)	0.90
Transseptal LVAD (TandemHeart)	19 (10.4)	37 (8.9)	0.60
Transaortic LVAD (Impella)	15 (8.2)	26 (6.2)	0.40
VA-ECMO	5 (2.7)	11 (2.6)	0.90
INTERMACS 1 or 2	84 (46.2)	190 (45.5)	0.80
Preoperative mean MELD score	14.9 ± 6.0	13.0 ± 5.3	<0.001
Preoperative medication use			
ACE inhibitors	94 (51.6)	244 (58.4)	0.10
Angiotensin II receptor blockers	36 (19.8)	68 (16.3)	0.30
Aldosterone antagonists	109 (59.9)	256 (61.2)	0.80
Calcium channel blockers	15 (8.2)	34 (8.1)	>0.99
Inotropes	144 (79.1)	335 (80.1)	0.80
Vasopressors	29 (15.9)	67 (16.0)	>0.99
Beta-blockers	125 (68.7)	306 (73.2)	0.30
Nitrates	80 (44.0)	199 (47.6)	0.40
Aspirin	137 (75.3)	314 (75.1)	>0.99
Preoperative laboratory values			
Serum creatinine, mg/dL	1.5 ± 0.8	1.4 ± 0.8	0.20
Neutrophil:lymphocyte ratio	6.7 ± 6.4	5.6 ± 5.7	0.04
Aspartate aminotransferase, U/L	58.9 ± 72.7	73.7 ± 211.0	0.40
Alanine aminotransferase, U/L	65.2 ± 121.7	80.9 ± 200.3	0.30
Serum albumin, g/dL	5.6 ± 7.5	4.6 ± 5.3	0.10
Total bilirubin, mg/dL	6.8 ± 44.5	1.7 ± 3.2	0.10
Preoperative hemodynamic data			
CVP, mm Hg	13.3 ± 7.4	11.4 ± 6.9	0.04
Pulmonary vascular resistance, WU	3.8 ± 4.2	3.7 ± 3.0	0.80
Pulmonary artery pulsatility index	3.3 ± 4.4	4.0 ± 4.1	0.20
Mean RAP/PCWP	0.52 ± 0.3	0.48 ± 0.3	0.30
Mean RAP/PCWP >0.54	56 (30.8)	113 (27.0)	0.40
CVP/PCWP	0.55 ± 0.3	0.5 ± 0.4	0.40
Intraoperative characteristics			
Concomitant procedures	49 (26.9)	119 (28.5)	0.90
LVAD type			0.20
HeartMate II	150 (82.4)	307 (73.4)	
HeartWare	29 (15.9)	97 (23.2)	
Other	3 (1.6)	14 (3.3)	
Cardiopulmonary bypass time, min	88.6 ± 51.9	81.3 ± 51.3	0.10

Values are n (%) or mean ± SD. ACE = angiotensin-converting enzyme; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CVP = central venous pressure; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LVAD = left ventricular assist device; MELD = Model for End-Stage Liver Disease; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; VA-ECMO = venoarterial extracorporeal membrane oxygenation.

TABLE 2 Postoperative Adverse Events in Patients Who Developed Postoperative Vasoplegia Compared With Patients Who Did Not

	Vasoplegia (n = 182)	No Vasoplegia (n = 418)	P Value
Acute kidney injury	35 (19.2)	77 (18.4)	0.90
Renal replacement therapy	27 (14.8)	68 (16.3)	0.80
Stroke	40 (22.0)	106 (25.4)	0.40
Reoperation for bleeding	51 (28.0)	93 (22.2)	0.10
Right heart failure	6 (3.3)	21 (5.0)	0.30
Early right ventricular assist device	2 (1.1)	10 (2.4)	0.30
Tracheostomy	27 (14.8)	60 (14.4)	0.90
Sepsis	62 (34.1)	131 (31.3)	0.50
Readmission	29 (15.9)	88 (21.1)	0.20
Length of stay (d)	43.9 ± 48.7	44.9 ± 68.0	0.90
Mortality			
30-d	18 (9.9)	29 (6.9)	0.20
60-d	27 (14.8)	42 (10.0)	0.09
90-d	33 (18.1)	53 (12.7)	0.08
1-y	62 (34.1)	128 (30.6)	0.40
Overall	86 (47.3)	206 (49.3)	0.60

Values are n (%) or mean ± SD.

Cox proportional survival analysis was performed with adjustment for factors previously associated with all-cause mortality in LVAD recipients (age, INTERMACS profile 1 or 2, preoperative dialysis) and for sex. $P < 0.05$ was considered statistically significant. Missing data were considered missing at random and were not imputed. Schoenfeld residual plots (not reported here) were performed for each covariate to ensure there was no strong evidence of violating the proportional hazards assumption.

The statistical analyses were performed using IBM SPSS Statistics for Macintosh, version 25 (SPSS Inc).

RESULTS

In all, 600 patients underwent implantation of a CF-LVAD device during the study period. At least 90% of the data were available for all variables except preoperative CVP (48.6% complete) and mean right atrial pressure (78.5% complete). The median follow-up was 3.2 years.

VASOPLEGIA VS NO VASOPLEGIA. Of the 600 patients, 182 (30.3%) developed postoperative vasoplegia within the first 24 hours. Two patients with vasoplegia had CVP >18 mm Hg but did not meet the prespecified definition of RVF. Within the postoperative vasoplegia group, 104 patients (57.1%; 17.3% of entire sample) had transient vasoplegia that resolved within 12 hours, and 78 patients (42.9%; 13.0% of entire sample) developed prolonged vasoplegia that lasted ≥ 12 hours.

Patients with postoperative vasoplegia were more likely to be male (89.6% vs 74.9%; $P < 0.001$) and had a higher body mass index (BMI) (31.7 ± 20.4 kg/m² vs 27.7 ± 6.4 kg/m²; $P = 0.01$) than patients who did not develop vasoplegia (Table 1). They were also more likely to have had preoperative stroke (20.3% vs 12.9%; $P = 0.047$) and preoperative dialysis (8.8% vs 4.3%; $P = 0.03$). Furthermore, patients with postoperative vasoplegia had a higher neutrophil:lymphocyte ratio (6.7 ± 6.4 vs 5.6 ± 5.7 ; $P = 0.04$) and a higher mean Model for End-Stage Liver Disease (MELD) score (14.9 ± 6.0 vs 13.0 ± 5.3 ; $P < 0.001$) than the no-vasoplegia patients. The type of CF-LVAD used did not differ between groups. The vasoplegia group had a nonsignificantly longer mean cardiopulmonary bypass time (88.6 ± 51.9 minutes vs 81.3 ± 51.3 minutes; $P = 0.10$) (Table 1).

The frequency of adverse events did not differ between the vasoplegia and no-vasoplegia groups (Table 2). Mortality was similar at 30 days (9.9% vasoplegia vs 6.9% no-vasoplegia; $P = 0.20$) but was nonsignificantly higher in the vasoplegia cohort at 60 days (14.8% vs 10.0%; $P = 0.09$) and 90 days (18.1% vs 12.7%; $P = 0.08$). Cox proportional survival estimates indicated similar all-cause survival in the any-vasoplegia and no-vasoplegia groups ($P = 0.40$; 95% CI: 0.9-1.4) after adjustment for age, INTERMACS profiles 1 and 2, preoperative dialysis, and sex.

PROLONGED VASOPLEGIA VS TRANSIENT VASOPLEGIA.

Compared with the transient-vasoplegia group, the prolonged-vasoplegia group had higher baseline serum creatinine levels (1.6 ± 0.9 vs 1.3 ± 0.6 ; $P = 0.01$) and a higher mean MELD (16.5 ± 6.2 vs 13.8 ± 5.7 ; $P = 0.003$) and more often had preoperative dialysis (14.1% vs 4.8%; $P = 0.03$) (Table 3). Preoperatively, the prolonged-vasoplegia group was less likely than the transient-vasoplegia group to be treated with angiotensin-converting enzyme inhibitors (ACEIs) (43.6% vs 57.7%; $P = 0.06$). No other differences in preoperative medication use were observed.

Patients with prolonged vasoplegia had higher rates of postoperative AKI (33.3% vs 18.3%; $P = 0.02$) and new postoperative renal replacement therapy (28.2% vs 13.5%; $P = 0.01$) than patients with transient vasoplegia (Table 4). Patients with prolonged vasoplegia also had higher 30-day (16.7% vs 5.8%; $P = 0.02$), 60-day (21.8% vs 9.6%; $P = 0.03$), and 90-day mortality (24.4% vs 13.5%; $P = 0.053$). Cox proportional survival estimates indicated worse all-cause overall survival in the prolonged-vasoplegia group ($P = 0.03$; 95% CI: 1.03-1.9) after adjustment

for age, INTERMACS profiles 1 and 2, preoperative dialysis, and sex (Figure 1).

Modified Poisson analysis revealed 4 risk factors for the development of postoperative vasoplegia (Table 5): male sex (RR: 1.99; 95% CI: 1.18-2.99; $P = 0.0006$), BMI (RR: 1.05; 95% CI: 1.03-1.07; $P < 0.001$), preoperative dialysis (odds ratio [OR]: 1.69; 95% CI: 1.09-2.65; $P = 0.02$), and preoperative MELD (OR: 1.04; 95% CI: 1.004-1.08; $P = 0.03$). In addition, 2 risk factors for prolonged vasoplegia were identified: the need for preoperative dialysis (OR: 2.39; 95% CI: 1.18-4.83, $P = 0.02$) and BMI (OR: 1.06; 95% CI: 1.03-1.1; $P < 0.001$).

DISCUSSION

In our cohort of CF-LVAD patients, 30% of patients developed postoperative vasoplegia, and 13% developed vasoplegia that lasted at least 12 hours. The main finding was that although development of postoperative vasoplegia was not associated with adverse outcomes, prolonged vasoplegia was associated with greater early mortality. Prolonged vasoplegia was also associated with greater likelihood of postoperative AKI (Central Illustration).

The general consensus among previous reports of vasoplegia after cardiac surgery is that vasoplegia is associated with higher mortality rates.¹⁻¹⁰ However, to our knowledge, few studies have focused specifically on the CF-LVAD population to capture the evolution of vasoplegia over time or have used immediate postoperative hemodynamic parameters to identify patients with postoperative vasoplegia. Our cohort of 600 patients compares favorably with the number of CF-LVAD patients in 4 previous studies of postoperative vasoplegia (Supplemental Table 1),^{2,4,10,16} which had samples ranging from 33 to 252 patients.

One challenge in interpreting the vasoplegia literature is heterogeneity among definitions, as highlighted in Supplemental Table 1. Cardiac index was used fairly consistent across the 4 studies, the threshold varying from 2.2 to 2.5 L/min/m². In contrast, SVR varied significantly across the studies. Tecson et al² and van Vessel et al¹⁰ each had no SVR requirement in their definitions of vasoplegia, whereas de Waal et al⁴ and Swan et al¹⁶ included either a MAP or an SVR threshold, rather than using both, to identify patients with vasoplegia. This may be problematic because the combination of SVR and a low MAP, as used in the current analysis, is essential for differentiating vasoplegic shock from shock of other causes. For example, in the recent study by Swan et al,¹⁶ 38% of the patients with vasoplegia had concomitant RVF.

TABLE 3 Baseline Characteristics of Patients Who Developed Transient Vasoplegia Compared With Prolonged Postoperative Vasoplegia

	Transient Vasoplegia (n = 104)	Prolonged Vasoplegia (n = 78)	P Value
Demographic data			
Male	93 (89.4)	70 (89.7)	0.70
Age	53.3 ± 13.1	54.4 ± 12.9	0.60
BMI, kg/m ²	31.7 ± 26.2	31.7 ± 7.4	0.10
Ischemic cardiomyopathy	44 (42.3)	38 (48.7)	0.70
Bridge to transplant	59 (56.7)	32 (41.0)	0.20
Past medical history			
Diabetes mellitus	48 (46.2)	33 (42.3)	0.60
Hypertension	66 (63.5)	52 (66.7)	0.40
COPD	14 (13.5)	10 (12.8)	0.90
Stroke	19 (18.3)	18 (23.1)	0.50
Dialysis	5 (4.8)	11 (14.1)	0.03
Previous cardiac surgery	37 (35.6)	31 (39.7)	0.50
Previous mechanical circulatory support	42 (40.4)	38 (48.7)	0.20
Intra-aortic balloon pump	40 (38.5)	46 (59.0)	0.90
Transseptal LVAD (TandemHeart)	17 (16.3)	7 (9.0)	0.60
Transaortic LVAD (Impella)	6 (5.8)	9 (11.5)	0.20
VA-ECMO	3 (2.9)	2 (2.6)	0.90
INTERMACS 1 or 2	46 (44.2)	38 (48.7)	0.60
Preoperative mean MELD score	13.8 ± 5.7	16.5 ± 6.2	0.003
Preoperative medication use			
ACE inhibitors	60 (57.7)	34 (43.6)	0.06
Angiotensin II receptor blockers	20 (19.2)	16 (20.5)	0.80
Aldosterone antagonists	59 (56.7)	50 (64.1)	0.50
Calcium channel blockers	9 (8.7)	6 (7.7)	0.80
Inotropes	81 (77.9)	63 (80.8)	0.30
Vasopressors	15 (14.4)	14 (17.9)	0.40
Beta-blockers	66 (63.5)	59 (75.6)	0.20
Nitrates	44 (42.3)	36 (46.2)	0.60
Aspirin	81 (77.9)	56 (71.8)	0.30
Preoperative laboratory values			
Serum creatinine, mg/dL	1.3 ± 0.6	1.6 ± 0.9	0.01
Neutrophil:lymphocyte ratio	6.3 ± 6.7	7.4 ± 6.1	0.30
Aspartate aminotransferase, U/L	55.6 ± 72.3	63.2 ± 73.6	0.80
Alanine aminotransferase, U/L	66.8 ± 138.6	63.1 ± 96.0	0.90
Serum albumin, g/dL	6.1 ± 8.3	4.9 ± 6.1	0.20
Total bilirubin, mg/dL	8.6 ± 57.8	4.3 ± 14.0	0.80
Preoperative hemodynamic data			
CVP, mm Hg	13.4 ± 7.8	13.1 ± 6.8	0.80
Pulmonary vascular resistance, WU	3.7 ± 4.6	3.9 ± 3.7	0.80
Pulmonary artery pulsatility index	3.4 ± 5.2	3.2 ± 3.0	0.90
Mean RAP/PCWP	0.5 ± 0.2	0.54 ± 0.3	0.40
Mean RAP/PCWP >0.54	31 (29.8)	25 (32.1)	0.80
CVP/PCWP	0.52 ± 0.3	0.58 ± 0.4	0.50
Intraoperative characteristics			
Concomitant procedures	27 (26.0)	22 (28.2)	0.40
LVAD type			0.30
HeartMate II	84 (80.8)	66 (84.6)	
HeartWare	17 (16.3)	12 (15.4)	
Other	3 (2.9)	0 (0.0)	
Cardiopulmonary bypass time, min	84.5 ± 54.1	94.2 ± 48.5	0.20

Values are n (%) or mean ± SD. Transient vasoplegia was defined as that lasting 6 to <12 hours; prolonged vasoplegia was defined as that lasting 12 to 24 hours.

ACE = angiotensin-converting enzyme; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CVP = central venous pressure; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LVAD = left ventricular assist device; MELD = Model for End-Stage Liver Disease; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; VA-ECMO = venoarterial extracorporeal membrane oxygenation.

TABLE 4 Postoperative Clinical Outcomes in Patients Who Developed Transient Vasoplegia Compared With Prolonged Postoperative Vasoplegia

	Transient Vasoplegia (n = 104)	Prolonged Vasoplegia (n = 78)	P Value
Acute kidney injury	19 (18.3)	26 (33.3)	0.02
Renal replacement therapy	14 (13.5)	22 (28.2)	0.01
Stroke	24 (23.1)	26 (33.3)	0.40
Early stroke	4 (3.8)	3 (3.8)	0.80
Reoperation for bleeding	26 (25.0)	25 (32.1)	0.40
Right heart failure	1 (1.0)	5 (6.4)	0.10
Early right ventricular assist device	0 (0)	2 (2.6)	0.20
Tracheostomy	15 (14.4)	12 (15.4)	>0.99
Sepsis	34 (32.7)	28 (35.9)	0.80
Readmission	15 (14.4)	14 (17.9)	0.50
Length of stay (d)	42.2 ± 47.1	46.2 ± 50.9	0.60
Mortality			
30-d	6 (5.8)	13 (16.7)	0.02
60-d	10 (9.6)	17 (21.8)	0.03
90-d	14 (13.5)	19 (24.4)	0.053
1-y	26 (29.8)	27 (39.7)	0.20
Overall	55 (52.9)	55 (70.5)	0.10

Values are n (%) or mean ± SD. Transient vasoplegia was defined as that lasting 6 to <12 hours; prolonged vasoplegia was defined as that lasting 12 to 24 hours.

Interestingly, although the other studies were strict about the number or doses of vasopressors required to identify patients with vasoplegia, the incidence of vasoplegia observed in our study (30%) was similar to those reported by van Vessem et al¹⁰ (29%) and De Waal et al⁴ (33%) but much lower than those reported by Tecson et al² (50%) and Swan et al¹⁶ (61%). Again, this difference may have been due to the inconsistent use of SVR and MAP in those other studies to capture patients with true vasoplegia. Swan et al,¹⁶ who reported the highest incidence of vasoplegia (61%), used a comparatively liberal definition of vasoplegia: an elevated MAP or SVR or a normal cardiac index, with norepinephrine equivalent requirements >0.1 µg/kg/min for at least 15 minutes. In contrast, to comprehensively identify patients with vasoplegia during the first 24 hours after CF-LVAD implantation, we incorporated a rigorous definition that required all hemodynamic thresholds to be met and included a strict vasopressor prerequisite. Our goal was to minimize other confounding causes, such as RVF, hemorrhagic shock, and hypovolemic shock.

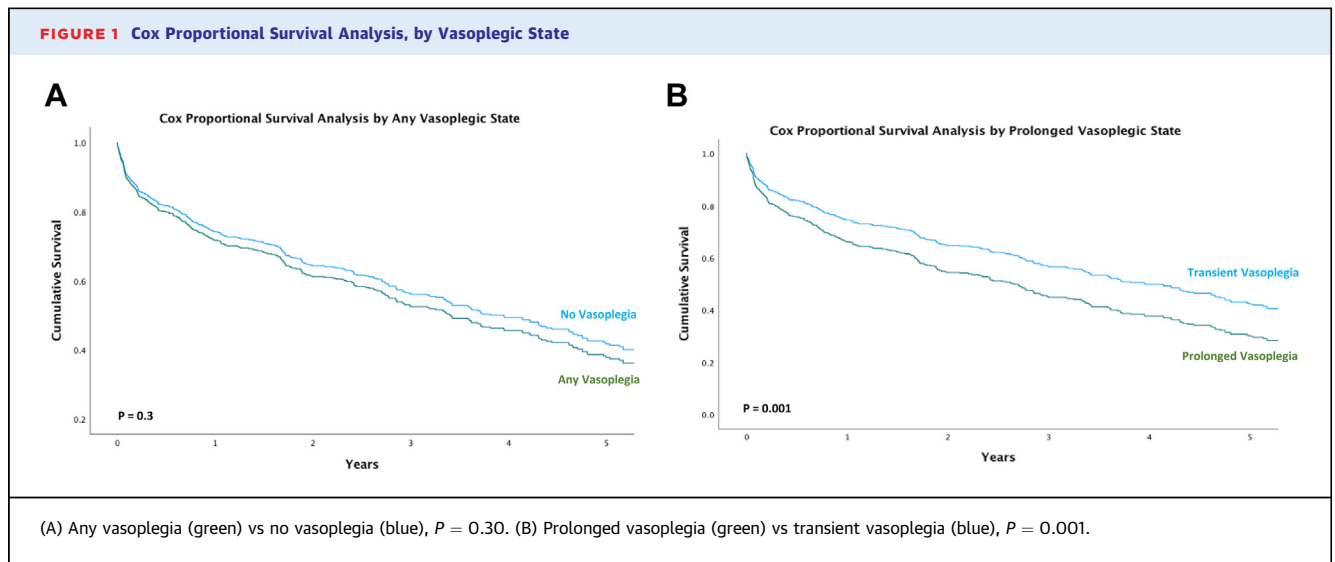
In our cohort, postoperative vasoplegia itself was not associated with early or long-term mortality, whereas prolonged vasoplegia was associated with both. Thus, studies that define vasoplegia according to hemodynamic parameters or vasopressors administered at the time of intensive care unit arrival may overestimate the incidence of vasoplegia or may

actually be identifying transient vasoplegia, which has less clinical significance than prolonged vasoplegia. In addition, whereas others have investigated vasoplegia 48 to 72 hours after implantation, multiple investigators have shown that the first 12 to 24 hours—the focus of our study—is the critical period for developing vasoplegia after CF-LVAD implantation.^{4,16}

Identifying patients at risk for prolonged vasoplegia may allow early risk stratification and intervention. We found that BMI, MELD score, and preoperative renal status were directly associated with whether a patient developed both postoperative vasoplegia in general and prolonged vasoplegia in particular. We did not find an association between preoperative use of ACEIs or angiotensin receptor blockers (ARBs) and the development of vasoplegia after CF-LVAD implantation; whereas other investigators¹⁰ have found an association between ACEIs or ARBs and postimplantation vasoplegia, most others did not find an association, including Tecson et al² after CF-LVAD implantation and Patarroyo et al¹ and Chan et al⁵ after heart transplant. In our analysis, 56% of patients received ACEIs and 17% received ARBs preoperatively; we typically hold these medications in patients presenting with higher-acuity INTERMACS profiles because of hemodynamic considerations.

Preoperative dialysis was a risk factor for any vasoplegia and for prolonged vasoplegia. Similarly, de Waal et al⁴ and Chan et al⁵ found that worsening renal function, as indicated by either the use of dialysis or increasing serum creatinine, was an independent predictor of vasoplegia development.^{4,5} Indeed, renal failure was the only preoperative risk factor for developing vasoplegia (OR: 1.47) identified by Dayan et al¹⁷ in a meta-analysis of 10 articles and more than 30,000 patients after cardiac surgery. It is not entirely clear whether the vasoplegia is exacerbating the AKI, the worsening AKI is prolonging the vasoplegia, or the renal replacement therapy is contributing to the ongoing vasopressor needs; in all likelihood, they are interrelated.¹⁸ Intraoperative strategies for reducing AKI in these patients include targeted perfusion strategies, such as goal-directed therapy, in addition to meticulous surgical technique to reduce the need for transfusions.¹⁹

Efforts to reduce postoperative AKI requiring renal replacement therapy after LVAD placement are critical, as AKI development is associated with a significant increase in mortality risk.²⁰ Although the exact pathophysiology of AKI remains unclear, a pivotal role has been identified for renally excreted inflammatory markers, including copeptin and bradykinin,



during the developmental stages of vasoplegia.^{21,22} The persistence of these inflammatory substances may perpetuate the vasodilatory state in patients with abnormal renal function. Our results indicating an association between obesity and prolonged vasoplegia may be related to pro-inflammatory adipokines.²³ Similar to results from a major randomized trial in cardiac surgery²⁴ and 2 other LVAD reports,^{2,10} we did not find an association between preoperative use of ARBs and the development of vasoplegia after CF-LVAD implantation. Moreover, although we had no information on the use of angiotensin receptor-neprilysin inhibitors in this patient cohort, others have not found an association between preoperative angiotensin receptor-neprilysin inhibitor use and postoperative vasoplegia after CF-LVAD implantation.²⁵

The MELD score also has been validated in multiple reports as a prognostic indicator for patients undergoing CF-LVAD implantation.^{26,27} Similar to van Vessem et al,¹⁰ we found a direct association between MELD score and vasoplegia risk. Other investigators also have found higher mortality rates after LVAD implantation in patients with MELD scores ≥ 14 .^{28,29} An elevated preoperative MELD score may reflect an elevated inflammatory state. Vasodilatory states involve higher levels of pro-inflammatory factors, including nitric oxide, interleukins (ILs) such as IL-1 and IL-6, tumor necrosis factor- α , and copeptin, and are exacerbated by receiving more blood transfusions.^{22,30,31} In states of worsening liver function, Kupffer cells, which are specialized hepatic macrophages, sometimes release inflammatory endotoxins and cytokines, including

IL-6.^{32,33} Furthermore, increased nitric oxide biosynthesis, which is commonly caused by hepatic failure, has been observed in portal-hypertensive states.³⁴ Higher MELD score can also be a reflection of congestive hepatopathy.³⁵ Because patients with elevated MELD scores are at higher risk for developing any vasoplegia and prolonged vasoplegia, further investigation into therapeutic interventions that could benefit these patients by mitigating that risk are warranted. Lastly, because CF-LVADs lack pulsatility, they may intrinsically increase the incidence of vasoplegia.³⁶

Transient vasoplegia was not associated with increased mortality in our study, whereas the progression to prolonged vasoplegia within the 12- to 24-hour window was associated with adverse outcomes. Therefore, early treatment of vasoplegia may offer a potential therapeutic target to prevent the development of prolonged vasoplegia.

When vasoplegia is severe, high doses of multiple vasopressors may be insufficient. In our practice, we begin by avoiding medications associated with vasoplegia (eg, propofol, milrinone³⁷). Our current pharmacological strategy after norepinephrine and vasopressin administration exceeds a norepinephrine equivalent dosage of 0.3 $\mu\text{g}/\text{kg}/\text{min}$ is to initiate angiotensin II.^{38,39} Once a MAP of 70 mm Hg is achieved and the other vasopressors are down-titrated, the angiotensin II is weaned off. We are mindful of maintaining a renal perfusion pressure (MAP-CVP) ≥ 60 mm Hg and adjusting hemodynamic targets accordingly to reduce the risk for AKI.⁴⁰ Patients at higher risk for developing postoperative prolonged vasoplegia may benefit from earlier administration of

TABLE 5 Risk Factors for Any Vasoplegia and Prolonged Vasoplegia After CF-LVAD Implantation

	RR	95% CI	P Value
Risk factors for any vasoplegia			
Sex	1.99	0.82-3.23	0.006
Preoperative dialysis	1.69	1.09-2.65	0.02
Cardiogenic shock (INTERMACS 1 or 2)	0.91	0.66-1.25	0.55
Vasopressors	1.15	0.80-1.65	0.46
Beta-blockers	0.8	0.60-1.07	0.13
Nitrates	0.92	0.70-1.22	0.59
Ischemic cardiomyopathy	0.96	0.70-1.32	0.85
Renin-angiotensin-aldosterone inhibitor use	0.83	0.57-1.23	0.33
Age, y	0.99	0.97-1.01	0.89
Body mass index, kg/m ²	1.05	1.03-1.07	<0.001
mRAP/PCWP	1.12	0.72-1.74	0.63
Cardiopulmonary bypass time, min	1.001	0.99-1.004	0.29
Albumin, g/dl	1.001	0.98-1.02	0.94
White blood cell count, 10 ⁹ /L	0.99	0.97-1.03	0.85
Neutrophil:lymphocyte ratio	1.02	0.99-1.04	0.08
Serum creatinine, mg/dL	0.77	0.58-1.03	0.08
Destination therapy	2.3	0.52-10.2	0.30
Model for End-Stage Liver Disease	1.04	1.004-1.08	0.03
Diabetes	0.93	0.70-1.25	0.63
Risk factors for prolonged vasoplegia			
Sex	1.96	0.85-4.48	0.11
Preoperative dialysis	2.39	1.18-4.83	0.02
Cardiogenic shock (INTERMACS 1 or 2)	0.94	0.56-1.57	0.81
Pressors	1.34	0.76-2.36	0.31
Beta-blockers	0.76	0.46-1.23	0.31
Nitrates	0.89	0.55-1.43	0.62
Ischemic cardiomyopathy	1.21	0.68-2.13	0.52
Renin-angiotensin-aldosterone inhibitor use	0.99	0.50-1.99	0.99
Age, y	1.01	0.99-1.03	0.65
Body mass index, kg/m ²	1.06	1.03-1.09	<0.001
mRAP/PCWP	1.3	0.65-2.60	0.45
Cardiopulmonary bypass time, min	1.003	0.99-1.01	0.13
Albumin, g/dl	0.99	0.95-1.04	0.81
White blood cell count, 10 ⁹ /L	0.97	0.91-1.04	0.41
Neutrophil:lymphocyte ratio	1.01	0.98-1.05	0.42
Serum creatinine	0.94	0.60-1.48	0.8
Destination therapy	1.8	0.43-8.7	0.63
Model for End-Stage Liver Disease	1.05	0.99-1.1	0.09
Diabetes	0.77	0.48-1.23	0.27

CF-LVAD = continuous-flow left ventricular assist device; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; mRAP/PCWP = mean right atrial pressure/pulmonary capillary wedge pressure; RR = relative risk.

angiotensin II or other therapeutic adjuncts to achieve a target MAP. Increasing data suggest that angiotensin II benefits patients with vasoplegic shock who need renal replacement therapy for AKI.⁴¹ We will occasionally use rescue measures, including glucocorticoids and mineralocorticoids, methylene blue, or hydroxycobalamin.^{42,43} In addition, lactic acidosis is treated aggressively with sodium

bicarbonate or, in severe cases, with renal replacement therapy as needed.

STUDY LIMITATIONS. This study was susceptible to the limitations of any single-institution retrospective report, despite having a larger sample size than the other CF-LVAD vasoplegia studies in the current literature. First, it is difficult to isolate vasoplegic shock completely, as there may have been an element of hemorrhagic shock or RVF in some patients. Moreover, some patients who presented with prolonged vasoplegia in the first 24 hours may have developed RVF later. Three of the other LVAD vasoplegia studies did not exclude patients with RVF,^{2,10,16} and 1 excluded patients who subsequently needed a right ventricular assist device.⁴ We recognize that vasoplegic shock may coexist with RVF in some patients or can lead to RVF in the early perioperative period. We attempted to minimize the confounding from RVF by including the high cardiac output and low SVR requirements characteristic of vasoplegia but not RVF. Moreover, chart abstraction was performed for every patient categorized as having vasoplegia, in order to confirm that concomitant RVF was not present.

Second, we did not have access to frequency of administration for adjunct therapies, such as glucocorticoids, methylene blue, and hydroxycobalamin, which are often used in the operating room to treat vasoplegia. However, the focus of this study was the development of vasoplegia and differences in outcomes with prolonged vasoplegia, as opposed to the efficacy of therapeutic strategies to mitigate the time course or severity of postoperative vasoplegia. These are areas we aim to investigate in future studies. Along those lines, although we had a substantial list of preoperative medications (Tables 2 and 4), we did not have data on the use of thyroid medications or on thyroid conditions in general. Third, our institution had not yet approved angiotensin II use during the study period; in our current practice, it is part of our vasopressor escalation algorithm. Fourth, we focused our analysis on the first 24 hours after surgery, but it is intuitive that patients who had prolonged vasoplegia beyond 24 hours probably had worse outcomes than those whose prolonged vasoplegia had resolved. Additionally, whereas this study was conducted before the HeartMate 3 (Abbott Laboratories) era, and earlier-generation CF-LVAD devices were used, the primary focus was early development of vasoplegia in the first 24 hours after surgery. Nearly a quarter of the patients in a study

CENTRAL ILLUSTRATION Impact of Prolonged Vasoplegia after Continuous-Flow Left Ventricular Assist Device Implantation

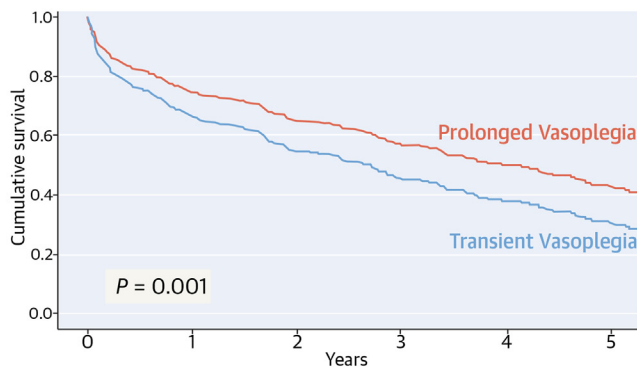
Study Methods

- 600 consecutive patients underwent continuous-flow left ventricular assist device (CF-LVAD) implantation
- Vasoplegia was defined as a mean arterial pressure ≤ 65 mm Hg, vasopressor need > 6 hours, CI ≥ 2.2 L/min/m², and an SVR < 800 dynes/s/cm⁵

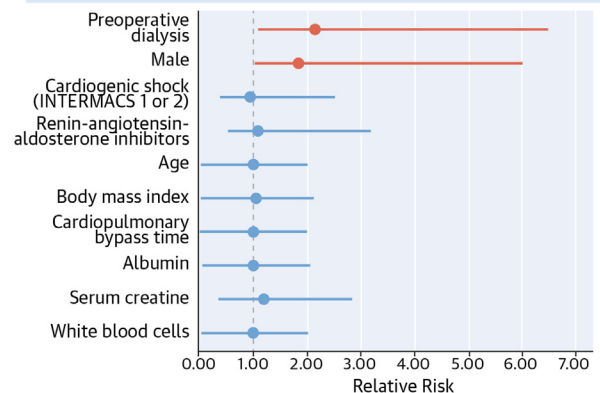
Results

- Transient vasoplegia (resolved in < 12 hours) occurred in 17.3% of patients
- Prolonged vasoplegia (lasting ≥ 12 hours) occurred in 13.0% of patients

Mortality Rate for Prolonged Vasoplegia vs Transient Vasoplegia



Relative Risks for Prolonged Vasoplegia



Conclusions

- Prolonged vasoplegia was associated with worse mortality
- Dialysis and male sex were associated with the highest relative risks of prolonged vasoplegia

Lamba HK, et al. JACC Adv. 2024;3(5):100916.

Patients who developed vasoplegia were grouped into those who had vasoplegia for < 12 hours (transient) or ≥ 12 hours (prolonged). Survival in patients with transient vasoplegia was comparable to survival in those with no vasoplegia; prolonged vasoplegia was associated with worse survival than no or transient vasoplegia. CI = cardiac index; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; SVR = systemic vascular resistance.

by Swan et al¹⁶ had a HeartMate 3, and no association was found between vasoplegia and type of LVAD. Therefore, while it is doubtful the specific device type significantly influences the incidence of prolonged vasoplegia, future studies with a higher proportion of HeartMate 3 recipients will be needed to support that claim. We believe that the lessons learned from this study are instructive for the current generation of CF-LVAD implants. Finally, in our analysis, we mitigated the effect of potential confounders by using multivariate analysis and domain knowledge; however, as is the case with all observational studies, we acknowledge that we cannot entirely eliminate the possibility of unmeasured or residual confounding.

CONCLUSIONS

Vasoplegia develops after CF-LVAD implantation in almost one-third of cases. Earlier recognition of this occurrence and identification of patients at higher risk for developing vasoplegia, including those with a higher MELD score, elevated BMI, or renal dysfunction, may allow for targeted therapeutic interventions to mitigate patients' risk of developing prolonged postoperative vasoplegia. Further investigation into early administration of aggressive treatments to mitigate the development of prolonged vasoplegia and reduce early mortality rates is warranted. Thoughtful patient selection and preoperative optimization should continue to be a focus.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Recognizing risk factors for prolonged vasoplegia can allow earlier identification of higher-risk patients and earlier initiation of therapeutic interventions. Prolonged vasoplegia is strongly associated with the development of AKI. Targeted strategies to reduce renal injury (preoperatively, intraoperatively, and postoperatively) are worthwhile.

TRANSLATIONAL OUTLOOK: This study represents a large series of patients who developed vasoplegia after left ventricular assist device implantation. Earlier identification of patients at higher risk for developing vasoplegia may allow for earlier intervention with pharmacological adjuncts, either preoperatively or intraoperatively, to curb the development of vasoplegia. Future directions include randomized trials using novel vasopressors or other adjuncts before vasoplegia develops to determine if prolonged postoperative vasoplegia can be mitigated.

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KEY WORDS health care, heart-assist devices, outcome assessment, postoperative complications, risk factors

APPENDIX For a supplemental table, please see the online version of this paper.