JACC: CARDIOVASCULAR IMAGING
VOL. 6, NO. 11, 2013
© 2013 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcmg.2013.06.006

ORIGINAL RESEARCH

Role of Echocardiography in Patients With Intravascular Hemolysis Due to Suspected Continuous-Flow LVAD Thrombosis

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OBJECTIVES This study sought to characterize the echocardiographic findings of patients presenting with intravascular hemolysis (IVH) due to suspected continuous-flow left ventricular assist device (LVAD) pump thrombosis.

BACKGROUND LVAD patients who develop pump thrombosis often present with IVH. Echocardiography may be able to detect device dysfunction in this setting.

METHODS Continuous-flow LVAD patients presenting with IVH due to suspected pump thrombosis were identified. Patients underwent echocardiography with cannula Doppler flow velocity interrogation. Findings were compared with baseline and follow-up studies, and with 49 stable LVAD control patients.

RESULTS Of 145 patients, 14 (10%) had IVH due to suspected pump thrombosis. The mean age was 55 ± 15 years, 93% were men, and 50% received LVAD as destination therapy. Mean duration between implantation and IVH was 231 ± 218 days. Eleven (79%) patients presented with hemoglobinuria, 9 (64%) with jaundice, and 5 (36%) with acute heart failure. Reduced cannula diastolic flow velocity and increased systolic/diastolic (S/D) flow velocity ratio were the only echocardiographic parameters significantly different from controls (outflow cannula 0.3 ± 0.2 m/s vs. 0.8 ± 0.3 m/s, $p = 0.03$, and 5.9 ± 2.8 vs. 1.7 ± 0.7, $p < 0.01$, respectively), and were worse for IVH patients with acute heart failure compared with those without (outflow cannula 0.2 ± 0.1 m/s vs. 0.5 ± 0.2 m/s, $p = 0.04$, and 7.2 ± 3.3 vs. 5.3 ± 2.0, $p = 0.02$, respectively). Outflow cannula diastolic flow velocity and S/D flow velocity ratio changed significantly from baseline ($p = 0.01$ and $p < 0.01$, respectively) in IVH patients, whereas systolic flow velocity did not change ($p = 0.59$). Odds ratios for outflow cannula diastolic flow velocity and S/D flow velocity ratio for predicting IVH were 0.60 (95% confidence interval [CI]: 0.51 to 0.73), $p = 0.02$, and 2.45 (95% CI: 2.37 to 2.52) $p < 0.01$, respectively. Corresponding inflow cannula values were similarly significant. Pump thrombosis was confirmed in 7 (50%) patients after LVAD retrieval.

CONCLUSIONS Reduced cannula diastolic flow velocity and increased S/D flow velocity ratio identified continuous-flow LVAD dysfunction in patients with IVH due to suspected pump thrombosis better than other echocardiographic parameters. (J Am Coll Cardiol Img 2013;6:1129–40) © 2013 by the American College of Cardiology Foundation

Continuous-flow left ventricular assist devices (LVAD) provide circulatory support and improve survival for patients with advanced heart failure (HF) (1–3). These devices have demonstrated improved durability and outcomes compared with older pulsatile LVADs, and currently are the preferred device model for patients with indications for LVAD implantation (1). Initially implanted as a bridge to transplantation (BTT), LVADs are increasingly used for the purpose of destination therapy (DT) (1).

Pump thrombosis is increasingly recognized as an important complication in patients supported by continuous-flow LVADs, and is associated with a high degree of morbidity and mortality (1,2,4). Patients with pump thrombosis frequently present with signs and symptoms of intravascular hemolysis (IVH) (1). Pump thrombosis may be associated with LVAD dysfunction impairing left ventricular (LV) unloading and circulatory support, and can lead to clinical HF and/or hemodynamic instability.

ABBREVIATIONS AND ACRONYMS

BTT = bridge to transplantation
DT = destination therapy
IAS = interatrial septum
IVH = intravascular hemolysis
IVS = interventricular septum
LAP = left atrial pressure
LVAD = left ventricular assist device
PI = pulsatility index
RAP = right atrial pressure
S/D = systolic/diastolic

Pump thrombosis is often diagnosed in the presence of clinical and biochemical signs of IVH, accompanied by changes in device parameters such as increased power levels. Echocardiography is an important tool for the evaluation of device and cardiac function in LVAD-supported patients (5), and echocardiographic parameters associated with adverse outcomes have been previously described (6). The role of echocardiography in the evaluation of patients presenting with IVH due to suspected pump thrombosis is poorly defined. The purpose of this study was to characterize the echocardiographic findings of patients presenting with IVH due to suspected continuous-flow LVAD pump thrombosis.

METHODS

Study population. We retrospectively reviewed the records of all patients with prior implantation of a HeartMate II continuous-flow LVAD (Thoratec Corporation, Pleasanton, California) followed at our center between January 2008 and December 2012. Patients implanted with an LVAD as either BTT or DT were included. Of 158 patients, we excluded 13 who died at the time of implantation or in the perioperative period, for a final study population of 145. All patients provided written informed consent granting access to their medical records for research purposes. The Mayo Clinic Institutional Review Board approved this study.

Intravascular hemolysis due to suspected LVAD pump thrombosis. Patients presenting with IVH due to suspected pump thrombosis were selected for further analysis. This was defined as an acute rise in serum lactate dehydrogenase ≥2-fold above the stable baseline level while on LVAD support in conjunction with elevated free plasma hemoglobin (>12 mg/dl) in the absence of other causes of hemolysis, accompanied by at least 1 of the following: 1) left-sided HF in the absence of other causes; or 2) acute or gradual increases in pump power of ≥2 W above the stable baseline level. Patients presenting with IVH due to suspected pump thrombosis were initially treated with intensified anticoagulation and then monitored for evidence of persistent or worsening IVH and/or end-organ dysfunction. Surgical device exchange or urgent heart transplantation was recommended for patients with signs of clinical or hemodynamic instability or worsening IVH and/or end-organ dysfunction. Intensified anticoagulation consisted of intravenous unfractionated heparin and intensified antiplatelet therapy with increased aspirin dose and/or addition of an oral platelet $P2Y_{12}$ receptor blocker. An intravenous glycoprotein IIb/IIIa inhibitor was added for patients with persistent clinical and/or biochemical IVH who remained stable without end-organ dysfunction.

Clinical and demographic data. The routine surveillance follow-up protocol after LVAD implantation at our institution has been previously described (6). Briefly, all patients underwent monthly clinical outpatient follow-up for the first 3 months after discharge from hospital, and then every 3 to 4 months thereafter unless otherwise indicated. Comprehensive clinical, laboratory, device, and echocardiographic data were collected at each surveillance encounter, and these data were also collected at the time of presentation with IVH due to suspected pump thrombosis. Device data included pump speed, power, flow, and pulsatility index (PI) (a measure of the magnitude of blood flow pulses

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Manuscript received April 12, 2013; revised manuscript received June 7, 2013, accepted June 13, 2013.

through the pump occurring with LV contraction). Echocardiographic data collected at IVH presentation were compared with baseline, defined as the most recent prior stable surveillance encounter. If a patient presented with IVH before a surveillance encounter occurred, data collected at the time of hospital discharge following LVAD implantation were considered baseline. Echocardiographic data at IVH presentation were also compared with the subsequent follow-up study after treatment.

Echocardiographic measurements. Transthoracic echocardiography was performed using a standardized LVAD clinical protocol using an iE33 (Philips Medical Systems, Andover, Maryland), Sequoia 512 (Siemens Medical Solutions, Malvern, Pennsylvania), or Vivid 7 or E9 (GE Healthcare, Milwaukee, Wisconsin) ultrasound system (5). LV intracavitary and wall thickness dimensions were measured using 2-dimensional imaging at the papillary muscle level from the parasternal short-axis view (7). Left ventricular ejection fraction (LVEF) was calculated by the Quinones method (8) assuming an akinetic apex, and LV mass was calculated by the method proposed by Devereux et al. (9). Mitral inflow deceleration time was measured using pulsed-wave (PW) Doppler flow imaging. Valvular regurgitation was qualitatively graded using color-flow Doppler imaging according to American Society of Echocardiography guidelines as follows: normal/trivial = 1; mild = 2; moderate = 3; and severe = 4 (10).

Right ventricular (RV) size and systolic function were evaluated in the apical 4-chamber view, and RV fractional area change was calculated as: (end-diastolic area minus the end-systolic area)/end-diastolic area × 100 (11). RV systolic dysfunction was graded qualitatively as none/normal, mild, moderate, or severe. RV function was also assessed by tricuspid annular plane systolic excursion measurement using M-mode imaging (11), and RV index of myocardial performance calculation, as previously described (12). Pulmonary artery systolic pressure (PASP) was estimated as: $(4 \times TRVmax^2)$ + estimated right atrial pressure (RAP), where TRVmax is the peak systolic continuous-wave Doppler flow velocity of tricuspid valve regurgitation at end-expiration. RAP estimation was based on interrogation of the inferior vena cava diameter and

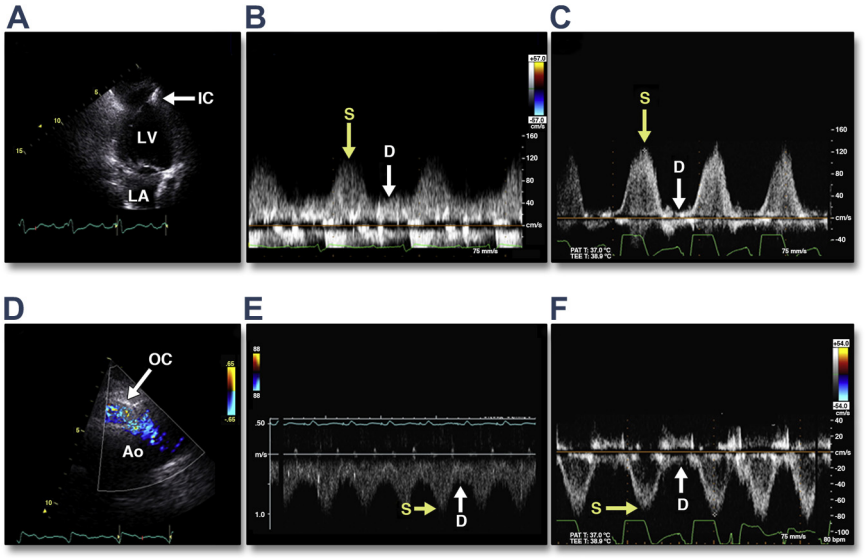

Figure 1. LVAD Inflow and Outflow Cannula With Doppler Flow Waveforms at Baseline and at Presentation With IVH Due to Suspected Pump Thrombosis

Echocardiographic images from a left ventricular assist device (LVAD)-supported patient: **(A)** apical 4-chamber view of the left ventricle (LV) with the inflow cannula (IC) visualized at the apex; **(B)** Doppler flow waveforms from the IC demonstrating systolic (S) **(yellow arrow)** and diastolic (D) **(white arrow)** flow velocities during normal device function; **(C)** flow velocities from the same patient at the time of presentation with intravascular hemolysis (IVH) due to suspected pump thrombosis demonstrating preserved systolic flow velocity with reduced diastolic flow velocity due to impaired device contribution to flow through the pump; **(D)** right-parasternal view of the outflow cannula (OC) showing flow into the aorta (Ao) from the same patient; **(E)** systolic and diastolic flow velocities from the OC during normal LVAD function; and **(F)** at the time of IVH due to suspected pump thrombosis, again illustrating preserved systolic with reduced diastolic flow velocities. LA = left atrium.

Table 1. Clinical, Laboratory, and LVAD Characteristics of LVAD Patients With IVH Due to Suspected Pump Thrombosis and Stable Control Patients

	IVH Patients (n = 14)	Controls (n = 49)	p Value
Clinical characteristics			
Age, yrs	55 ± 15	57 ± 13	0.48
Male	13 (93)	45 (92)	0.61
Hypertension	6 (43)	19 (39)	0.17
Diabetes mellitus	7 (50)	12 (24)	**0.05**
Chronic renal insufficiency	7 (50)	22 (45)	0.29
Atrial fibrillation	4 (29)	13 (27)	0.55
Cardiomyopathy etiology			0.36
Ischemic	6 (43)	23 (47)	
Dilated	6 (43)	27 (55)	
Valvular	1 (7)	0 (0)	
Sarcoidosis	1 (7)	0 (0)	
Body mass index, kg/m^2	30 ± 5	29 ± 5	0.84
Heart rate, beats/min	88 ± 11	75 ± 15	**0.04**
Blood pressure, systolic or mean, mm Hg	84 ± 15	89 ± 12	0.11
Laboratory characteristics			
Hemoglobin, g/dl	9.1 ± 3.0	12.3 ± 1.7	**<0.01**
Platelets, 10^9/l	157 ± 175	209 ± 164	**<0.01**
Bilirubin, mg/dl	1.9 ± 0.8	1.1 ± 0.1	**0.02**
AST, U/l	198 ± 137	57 ± 84	**<0.01**
ALT, U/l	271 ± 162	68 ± 79	**<0.01**
Lactate dehydrogenase, U/l	2,273 ± 1,418	367 ± 138	**<0.01**
Plasma hemoglobin, mg/dl	48.6 ± 23.7	11.8 ± 9.4	**<0.01**
INR	1.2 ± 0.9	1.9 ± 0.5	**0.03**
Creatinine, mg/dl	2.7 ± 1.8	1.3 ± 0.4	**0.01**
Blood urea nitrogen, mg/dl	42 ± 14	20 ± 7	**<0.01**
Albumin, g/dl	3.4 ± 0.8	3.6 ± 0.5	0.09
NT-proBNP, pg/ml	2,189 ± 1,208	358 ± 591	**<0.01**
LVAD characteristics			
Time since implant, days	231 ± 218	269 ± 309	0.07
Destination therapy	7 (50)	23 (47)	0.61
Pump speed, rpm	9,507 ± 421	9,483 ± 306	0.57
Pump flow, l/min	5.2 ± 1.7	5.5 ± 0.8	0.20
Pump power, W	7.2 ± 3.6	4.9 ± 1.9	**<0.01**
Pulsatility index	2.8 ± 2.6	4.8 ± 1.1	**<0.01**

Values are mean ± SD or n (%). p values in **bold** are statistically significant.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; IVH = intravascular hemolysis; LVAD = left ventricular assist device; NT-proBNP = amino terminal pro–B-type natriuretic peptide; rpm = rotations per minute.

distensibility, and scored as 5, 10, 15, or 20 mm Hg, as previously described (13).

LVAD echocardiographic measurements. LVAD specific echocardiographic measurements performed on all patients included 2-dimensional visualization and interrogation of the inflow and outflow cannula using color-flow and continuous-wave or PW Doppler flow imaging as previously described (5,6,14). The inflow cannula was evaluated from the apical 4- and 2-chamber views (Fig. 1). The outflow cannula was evaluated from the high left parasternal long-axis view or right parasternal view (with the patient in right lateral decubitus position) (Fig. 1). Off-axis imaging was sometimes required. The LVAD echocardiography protocol used at our laboratory includes documentation in the final report of the optimal transthoracic acoustic imaging windows used for measuring cannula Doppler flow velocities, thereby aiding serial assessment. Peak systolic and nadir diastolic flow velocities were measured for both the inflow and outflow cannulas (Fig. 1), and the ratio of systolic/diastolic (S/D) flow velocity was calculated (5).

LVAD output was estimated using the product of the outflow cannula PW Doppler velocity–time integral, and the calculated cross-sectional area from the cannula diameter measured in the imaging views described earlier in the text (6,15). Total cardiac output (the sum of LVAD output and native LV output) was estimated using the product of the RV outflow tract PW Doppler velocity-time integral and the calculated cross-sectional area from the RV outflow tract diameter measured from the parasternal short-axis view (11). Measures of LV unloading included: end-diastolic interventricular septum (IVS) position (neutral, shifted leftward or rightward), and aortic valve (AV) opening frequency (closed, opens intermittently, or opens every cardiac cycle). Mean left atrial pressure (LAP) was estimated based on estimated RAP and the end-diastolic interatrial septum (IAS) position: LAP = RAP if IAS is neutral, LAP = RAP − 5 if IAS is shifted leftward, and LAP = RA P + 5 if IAS is shifted rightward, as previously described (6).

Statistical analysis. Data are presented as the mean ± SD for continuous data or as frequency and percentages for categorical data. Patients with IVH due to suspected pump thrombosis were compared to a selected sample of 49 of 52 eligible stable LVAD control patients (3 were excluded due to suboptimal image quality) matched with IVH patients by age, sex, and goal of LVAD therapy (BTT or DT). Comparisons between patient groups were performed using the Student *t* test or Wilcoxon rank sum test for normally and non-normally distributed data for continuous variables, respectively, and the Fisher exact test for categorical variables. Data normality was assessed using the Shapiro-Wilk test. Changes in echocardiographic variables at different

time points were compared using the Wilcoxon signed rank test or paired Student *t* test as indicated. Odds ratios with 95% confidence intervals were calculated for the association of echocardiographic variables with IVH due to suspected pump thrombosis. Correlations between echocardiographic variables and device parameters in IVH patients were evaluated according to the Pearson correlation coefficient (r). All p values were 2-sided, and a value of $p \leq 0.05$ was considered statistically significant. Statistical analyses were performed using JMP version 9.0 statistical software (SAS Institute Inc., Cary, North Carolina).

RESULTS

Patient characteristics. Of 145 patients in the study population, 14 (10%) had IVH due to suspected pump thrombosis. Clinical, laboratory, and device characteristics of IVH and stable LVAD control patients are presented in Table 1. The mean age of IVH patients was 55 ± 15 years, 93% were men, and 50% received LVAD as DT. The mean time between LVAD implantation and IVH was 231 ± 218 days. Twelve (86%) IVH patients presented with subtherapeutic international normalized ratio levels; 5 cases occurred following interruption of anticoagulation due to a recent bleeding event, and 2 in anticipation of an elective procedure. Two patients developed IVH despite therapeutic international normalized ratio levels. All patients had biochemical evidence of IVH (Table 1), 11 presented with hemoglobinuria and 9 with jaundice. Ten (71%) patients presented with device parameter abnormalities, including 10 with increased power levels and 9 with decreased PIs.

Echocardiographic characteristics. Echocardiographic characteristics of IVH and stable LVAD control patients are presented in Table 2. IVH patients trended towards having larger LVs, worse LVEF, and lower mitral inflow deceleration times compared with control patients. Measures of RV enlargement and systolic function were also worse in IVH patients, and estimated PASP was higher.

LVAD echocardiographic characteristics. LVAD-specific echocardiographic measurements were feasible in all IVH patients and are compared with the measurements in stable LVAD control patients in Table 2. Although systolic velocities were similar between groups for both the inflow and outflow cannulas, diastolic velocities were significantly lower for IVH patients, suggesting impaired device contribution to flow through the pump (Fig. 1). This resulted in a significantly higher S/D velocity ratio for the inflow ($p = 0.01$) and outflow ($p < 0.01$) cannulas. Estimated LVAD and total cardiac output trended towards being lower for IVH patients, who also more often had a rightward IVS shift and AV opening, both reflecting less efficient LV unloading. IAS position and estimated LAP were similar between groups.

Because patients who presented with acute decompensated HF at the time of IVH due to suspected pump thrombosis were felt to have more clinically significant LVAD dysfunction and impaired LV unloading, echocardiographic characteristics of IVH patients presenting with ($n = 5$) and without ($n = 9$) acute HF were compared (Table 3). Acute HF was defined as the presence of new pulmonary edema and/or pleural effusions on chest x-ray, or the need for either intravenous diuretics or inotrope therapy. Patients with acute HF trended towards having larger LVs and lower LVEF than those without HF. Patients with acute HF had lower diastolic velocities for the inflow and outflow cannulas in addition to higher S/D velocity ratios, although this difference was only significant for the outflow cannula ($p = 0.04$ and $p = 0.02$, respectively). In keeping with less efficient LV unloading, IVH patients with acute HF trended towards having a more rightward IVS shift and regular AV opening than those without.

Cannula diastolic velocity and S/D velocity ratio correlated with device power level for IVH patients (inflow cannula: diastolic velocity $r = 0.73$, $p = 0.04$; S/D velocity ratio $r = 0.70$, $p = 0.04$; outflow cannula: diastolic velocity $r = 0.79$, $p = 0.02$; S/D velocity ratio $r = 0.81$, $p < 0.01$), whereas only S/D velocity ratios correlated with PI (inflow cannula: $r = 0.77$, $p = 0.03$; outflow cannula: $r = 0.78$, $p = 0.01$). No other echocardiographic parameters correlated with device power or PI (Online Table 1).

Treatment and outcomes. All patients were hospitalized at IVH presentation and treated with intensified anticoagulation. IVH resolved without complication in 7 (50%) patients with intensified anticoagulation. Of the remaining 7 patients: 1 went for urgent device exchange surgery, 2 declined urgent device exchange surgery (both were DT LVAD patients) and subsequently died (1 due to intracranial hemorrhage and 1 severe HF), and 4 went for urgent heart transplantation. All 5 patients who went for device exchange or heart transplantation survived. Pump thrombus was confirmed by inspection in all 7 patients undergoing device explantation. Patients who required

Table 2. Echocardiographic Characteristics of LVAD Patients With IVH Due to Suspected Pump Thrombosis and Stable Control Patients

	IVH Patients (n = 14)	Controls (n = 49)	p Value
Standard echocardiographic parameters			
LV end-diastolic diameter, mm	64 ± 8	60 ± 9	0.18
LV end-systolic diameter, mm	53 ± 11	51 ± 10	0.52
LV septal wall thickness, mm	10 ± 2	9 ± 3	0.70
LV posterior wall thickness, mm	10 ± 3	10 ± 3	0.75
LV ejection fraction, %	24 ± 9	28 ± 15	0.23
LV mass, g	290 ± 176	308 ± 199	0.82
Mitral inflow deceleration time, ms	142 ± 79	164 ± 90	0.07
Mitral inflow deceleration time <150 ms	8 (57)	20 (41)	0.08
Aortic regurgitation grade	1/4	1/4	0.60
Aortic regurgitation >trivial	4 (29)	12 (24)	0.72
Mitral regurgitation grade	1/4	1/4	0.81
Mitral regurgitation >mild	3 (21)	9 (18)	0.73
RV end-diastolic area, cm^2	31 ± 8	29 ± 6	0.21
RV end-systolic area, cm^2	22 ± 8	19 ± 7	0.39
RV fractional area change, %	29 ± 15	32 ± 12	0.23
RV ≥ moderate enlargement	8 (57)	15 (31)	**0.03**
RV ≥ moderate systolic dysfunction	9 (64)	16 (33)	**0.01**
TAPSE, mm	15 ± 4	18 ± 6	0.32
RIMP	0.37 ± 0.24	0.28 ± 0.13	0.20
Tricuspid regurgitation grade	2/4	1/4	0.28
Tricuspid regurgitation >mild	6 (43)	18 (37)	0.33
Tricuspid regurgitation velocity, m/s	2.5 ± 0.3	2.3 ± 0.3	0.44
Estimated RAP, mm Hg	12 ± 5	9 ± 4	0.25
Estimated PASP, mm Hg	40 ± 18	33 ± 15	0.27

Continued on the next page

device removal had lower diastolic velocities for the inflow (0.1 ± 0.1 m/s vs. 0.3 ± 0.1 m/s, $p = 0.06$) and outflow (0.1 ± 0.1 m/s vs. 0.4 ± 0.1 m/s, $p = 0.03$) cannula, and higher S/D velocity ratios for the inflow (3.3 ± 1.1 vs. 2.6 ± 0.8, $p = 0.02$) and outflow (7.5 ± 2.7 vs. 5.0 ± 1.9, $p < 0.01$) cannulas than those who improved with intensified anticoagulation.

Serial echocardiographic characteristics. Serial echocardiographic characteristics for IVH patients are presented in Table 4. The mean duration between echocardiograms performed at baseline and IVH presentation was 127 ± 82 days, and between the IVH and follow-up studies, was 76 ± 21 days. The 2 patients who died and 1 who had urgent device exchange surgery did not have follow-up echocardiography available for comparison. In comparison with baseline, 13 (93%) patients had reduced inflow and outflow cannula diastolic velocities at IVH presentation, all of whom also had increased S/D velocity ratios. Among patients with follow-up echocardiography, improvements in both parameters were observed in 10 patients (91%). By comparison, 8 (57%) patients had increased LV end-diastolic diameter and 4 (29%) had increased frequency of AV opening from baseline to IVH presentation, with follow-up improvement occurring in 3 and 2 patients, respectively.

Mean inflow and outflow cannula diastolic velocities (Fig. 2) and S/D velocity ratio (Fig. 3) significantly declined and increased, respectively, from baseline to IVH presentation, and generally returned close to baseline values in follow-up (Table 4). By comparison, diastolic velocity (Fig. 2) and S/D velocity ratio (Fig. 3) did not significantly change in stable LVAD control patients over time. Serial changes in other parameters reflecting LVAD function and LV unloading were not statistically

Table 2. Continued

	IVH Patients (n = 14)	Controls (n = 49)	p Value
LVAD echocardiographic parameters			
Inflow cannula systolic flow velocity, m/s	0.8 ± 0.3	0.9 ± 0.3	0.72
Inflow cannula diastolic flow velocity, m/s	0.2 ± 0.2	0.6 ± 0.4	**0.01**
Inflow cannula systolic/diastolic flow velocity ratio	2.9 ± 1.4	1.6 ± 0.7	**0.01**
Outflow cannula systolic flow velocity, m/s	1.5 ± 0.3	1.6 ± 0.5	0.59
Outflow cannula diastolic flow velocity, m/s	0.3 ± 0.2	0.8 ± 0.3	**0.03**
Outflow cannula systolic/diastolic flow velocity ratio	5.9 ± 2.8	1.8 ± 0.7	**<0.01**
LVAD output, l/min	4.3 ± 2.1	4.9 ± 1.3	0.28
Total cardiac output, l/min	4.8 ± 2.2	5.6 ± 1.6	0.20
Interventricular septum position			0.18
Rightward	3 (21)	2 (4)	
Neutral	10 (71)	41 (84)	
Leftward	1 (8)	6 (12)	
Aortic valve opening frequency			0.20
Closed	7 (50)	35 (71)	
Opens intermittently	3 (22)	11 (23)	
Opens	4 (28)	3 (6)	
Interatrial septum position			0.25
Rightward	2 (14)	2 (4)	
Neutral	11 (79)	39 (80)	
Leftward	1 (7)	8 (16)	
Estimated LAP, mm Hg	11 ± 5	9 ± 5	0.31

Values are mean ± SD or n (%). p values in **bold** are statistically significant.
LAP = left atrial pressure; LV = left ventricular; PASP = pulmonary artery systolic pressure; RAP = right atrial pressure; RIMP = right ventricular index of myocardial performance; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; other abbreviations as in Table 1.

significant in IVH patients (Table 4). Lastly, odds ratios with 95% confidence intervals associating echocardiographic parameters with IVH due to suspected pump thrombosis are presented in Table 4. The diastolic velocity and S/D velocity ratio were significantly associated with IVH for both the inflow and outflow cannulas.

DISCUSSION

This study demonstrates that patients with HeartMate II (Thoratec Corporation) continuous-flow LVADs presenting with IVH due to suspected pump thrombosis have distinct echocardiographic findings that differentiate them from stable LVAD patients. Most significant among these are reduced cannula diastolic velocity with preserved systolic velocity, resulting in an increased S/D velocity ratio. Serial echocardiograms in IVH patients showed that cannula diastolic velocity and S/D velocity ratio abnormalities were greater at the time of IVH in comparison with baseline and improved with resolution of the clinical syndrome after treatment. We also found that these parameters were more abnormal in IVH patients presenting with acute HF and in those requiring device removal, likely reflecting a greater degree of LVAD dysfunction.

This study provides important insights into the interpretation of Doppler flow waveforms acquired from the inflow and outflow cannula during echocardiography in continuous-flow LVAD patients. A continuous signal with systolic peaks and diastolic nadirs reflects the characteristic blood flow pattern through the pump that is the hallmark of continuous-flow devices. LV contraction increases blood flow through the pump, resulting in an increased systolic cannula velocity. Diastolic velocity is independent of LV contraction and reflects flow through the pump that is generated by the LVAD alone. This explains why in the setting of suspected pump thrombus and device dysfunction, diastolic flow is the predominant waveform affected,

Table 3. Echocardiographic Characteristics of LVAD Patients With IVH Due to Suspected Pump Thrombosis Presenting With and Without Acute HF

	IVH Patients With Acute HF (n = 5)	IVH Patients Without Acute HF (n = 9)	p Value
LV end-diastolic diameter, mm	64 ± 9	62 ± 8	0.15
LV end-systolic diameter, mm	53 ± 10	52 ± 12	0.67
LV ejection fraction, %	23 ± 9	25 ± 9	0.82
Mitral inflow deceleration time, ms	140 ± 88	146 ± 72	0.20
Estimated PASP, mm Hg	40 ± 18	39 ± 17	0.42
Inflow cannula systolic flow velocity, m/s	0.8 ± 0.3	0.9 ± 0.4	0.94
Inflow cannula diastolic flow velocity, m/s	0.2 ± 0.1	0.3 ± 0.1	0.74
Inflow cannula systolic/diastolic flow velocity ratio	3.1 ± 1.6	2.8 ± 1.3	0.12
Outflow cannula systolic flow velocity, m/s	1.4 ± 0.2	1.5 ± 0.6	0.83
Outflow cannula diastolic flow velocity, m/s	0.2 ± 0.1	0.5 ± 0.2	**0.04**
Outflow cannula systolic/diastolic flow velocity ratio	7.2 ± 3.3	5.3 ± 2.0	**0.02**
LVAD output, l/min	4.3 ± 2.1	4.2 ± 1.8	0.64
Total cardiac output, l/min	4.1 ± 2.0	5.5 ± 2.4	0.16
Interventricular septum position			0.28
Rightward	3	0	
Neutral	2	8	
Leftward	0	1	
Aortic valve opening frequency			0.11
Closed	0	7	
Opens intermittently	2	1	
Opens	3	1	
Interatrial septum position			0.75
Rightward	1	1	
Neutral	4	7	
Leftward	0	1	
Estimated LAP, mm Hg	11 ± 3	12 ± 6	0.88

Values are mean ± SD or n. p values in **bold** are statistically significant.
HF = heart failure; other abbreviations as in Tables 1 and 2.

with the degree of reduction likely reflecting the degree of thrombus interference with pump function. Systolic velocity is less affected, and in our study, was relatively preserved in most patients despite reduced diastolic velocity. In the setting of worsening LV contractility, systolic velocity will fall. The observed correlation between LVAD PI and cannula S/D velocity ratio reinforces this principle because both parameters reflect the device's relative contribution to flow through the pump along with changes in loading conditions.

Our study demonstrates that LVAD cannula Doppler flow interrogation is a useful noninvasive tool for evaluating patients with IVH due to suspected pump thrombosis, particularly when values can be compared with previous echocardiograms performed during periods of normal device function. Cannula diastolic velocity and S/D velocity ratio could potentially be used to grade the severity of device dysfunction when pump thrombosis is suspected. The finding of improvement in these parameters following treatment with intensified anticoagulation suggests they could be used to assess response to treatment in patients who do not require urgent surgical device exchange. The utility of these parameters for guiding therapy in this setting warrants further research.

This is the first study, to our knowledge, to report comprehensive serial echocardiographic findings in LVAD patients with IVH due to suspected pump thrombosis. Our center previously described ranges of multiple echocardiographic variables in stable

Table 4. Serial Echocardiographic Findings in LVAD Patients Presenting With IVH Due to Suspected Pump Thrombosis and Odds Ratios of Echocardiographic Parameters for Predicting IVH

	Baseline (n = 14)	IVH (n = 14)	Follow-Up (n = 11)	p Value*	OR (95% CI, p Value)
LV end-diastolic diameter, mm	62 ± 7	64 ± 8	63 ± 10	0.43	1.19 (0.89–1.42, p = 0.27)
LV end-systolic diameter, mm	51 ± 9	53 ± 11	53 ± 10	0.92	1.05 (0.78–1.22, p = 0.31)
LV ejection fraction, %	22 ± 10	23 ± 9	22 ± 8	0.74	1.14 (0.82–1.35, p = 0.37)
Mitral inflow deceleration time, ms	149 ± 90	142 ± 79	145 ± 99	0.19	0.71 (0.34–1.17, p = 0.29)
Estimated PASP, mm Hg	36 ± 16	40 ± 18	37 ± 17	0.35	1.21 (0.95–1.37, p = 0.21)
Inflow cannula systolic flow velocity, m/s	0.8 ± 0.4	0.8 ± 0.3	0.9 ± 0.4	0.77	1.02 (0.73–1.11, p = 0.18)
Inflow cannula diastolic flow velocity, m/s	0.5 ± 0.3	0.2 ± 0.1	0.4 ± 0.2	**0.02**	**0.69 (0.58–0.77, p = 0.03)**
Inflow cannula systolic/diastolic flow velocity ratio	1.6 ± 0.5	2.9 ± 1.4	2.0 ± 0.6	**<0.01**	**2.01 (1.82–2.21, p < 0.01)**
Outflow cannula systolic flow velocity, m/s	1.5 ± 0.4	1.5 ± 0.3	1.4 ± 0.2	0.59	1.07 (0.73–1.14, p = 0.24)
Outflow cannula diastolic flow velocity, m/s	0.7 ± 0.2	0.3 ± 0.1	0.6 ± 0.2	**0.01**	**0.60 (0.51–0.73, p = 0.02)**
Outflow cannula systolic/diastolic flow velocity ratio	2.0 ± 0.3	5.9 ± 3.8	2.6 ± 0.3	**<0.01**	**2.45 (2.37–2.52, p < 0.01)**
LVAD output, l/min	4.6 ± 2.7	4.3 ± 2.1	4.4 ± 2.7	0.15	0.87 (0.62–1.16, p = 0.30
Total cardiac output, l/min	5.0 ± 3.1	4.8 ± 2.2	4.9 ± 2.5	0.30	0.92 (0.70–1.23, p = 0.42)
Interventricular septum position				0.28	1.10 (0.73–1.30, p = 0.37)
Rightward	0 (0)	2 (14)	0 (0)		
Neutral	13 (93)	11 (79)	10 (91)		
Leftward	1 (7)	1 (7)	1 (9)		
Aortic valve opening frequency				0.25	1.21 (0.90–1.41, p = 0.10)
Closed	10 (58)	7 (50)	9 (82)		
Opens intermittently	4 (28)	3 (22)	1 (9)		
Opens	0 (14)	4 (28)	1 (9)		
Interatrial septum position				0.23	1.13 (0.79–1.24, p = 0.31)
Rightward	0 (0)	1 (7)	0 (0)		
Neutral	11 (79)	11 (79)	10 (91)		
Leftward	3 (21)	2 (14)	1 (9)		
Estimated LAP, mm Hg	10 ± 3	11 ± 5	11 ± 4	0.40	1.02 (0.54–1.29, p = 0.19)

Values are mean ± SD or n (%). Values in **bold** are statistically significant. *Comparison of baseline and IVH presentation values.
CI = confidence interval; OR = odds ratio; other abbreviations as in Tables 1 and 2.

patients with normally functioning HeartMate II (Thoratec Corporation) LVADs, including systolic and diastolic velocities for both the inflow and outflow cannulas (5). Topilsky et al. (6) later described echocardiographic variables associated with poor 90-day outcomes following LVAD implantation. That study found that measures of RV systolic function and measures of LV unloading, including mitral inflow deceleration time, estimated LAP, and IAS position, predicted outcome. None of those variables were significantly associated with IVH due to suspected pump thrombosis in our study, even though this condition can also lead to impaired LV unloading. This difference may be due to a smaller number of patients included in our study. Their study also included patients with normally functioning LVADs, unlike patients in our study who likely had varying degrees of device dysfunction. Accordingly, adverse outcomes in their study were largely due to RV failure or bleeding complications (1 patient died from embolic stroke, although it is not clear whether that patient also had device thrombosis). We found cannula Doppler flow interrogation to be more accurate in the setting of suspected pump thrombosis, variables that were not evaluated in their study. Neither study found LV dimensions, LVEF, AV opening frequency, or calculated LVAD or total cardiac output were significantly associated with outcome.

The recently published Ramp study (4) describes a standardized protocol for optimizing LVAD pump speed based on graded speed increases under

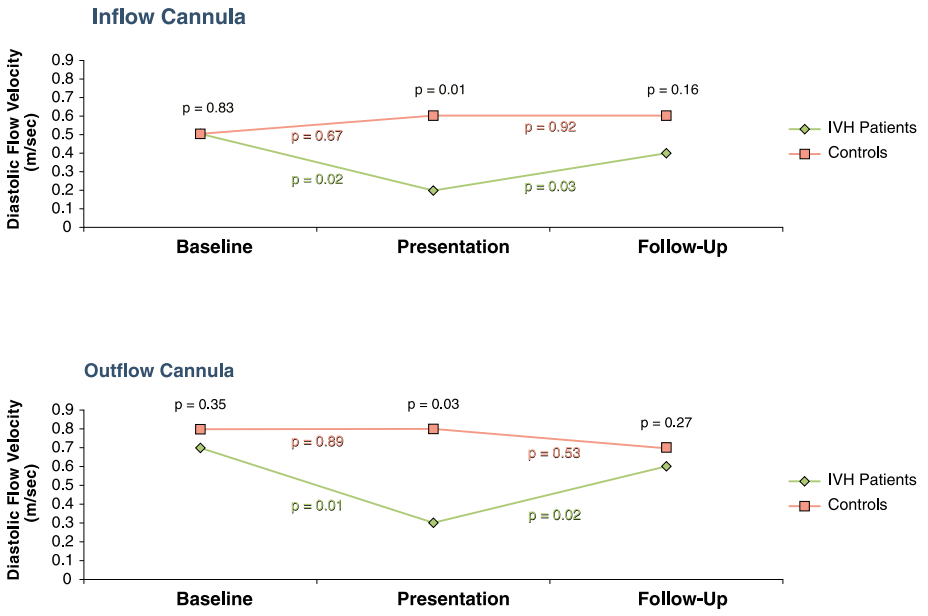

Figure 2. Serial LVAD Inflow and Outflow Cannula Diastolic Flow Velocities in IVH Patients and Stable LVAD Control Patients

Comparison of serial diastolic Doppler flow velocities from the inflow **(top)** and outflow **(bottom)** cannula in LVAD patients with IVH due to suspected pump thrombosis **(green)** and stable LVAD control patients **(pink)** at baseline, at presentation, and in follow-up. p values above the curves **(black)** compare values between IVH and control patients, whereas p values below the curves compare serial measurements at different time points for IVH **(green)** and control **(pink)** patients. Abbreviations as in Figure 1.

echocardiographic guidance. Changes in echocardiographic variables along with device parameters are recorded after each pump speed increase, and the slope of each parameter's linear function plot is used to select the pump speed that optimizes LV unloading. This protocol proved safe and effective for 39 patients with HeartMate II (Thoratec Corporation) LVADs included in the study. The protocol was also shown to be accurate for the detection of pump thrombosis when used in combination with lactate dehydrogenase levels in 17 patients with suspected pump thrombosis. Although the use of echocardiography-guided ramp studies is generally recommended in the literature for optimizing pump speed in LVAD patients (16), their use in the setting of suspected pump thrombosis varies widely among LVAD implanting centers. We present a different and possibly complementary echocardiographic approach for detecting device dysfunction due to pump thrombosis that can be performed quickly and without the need for multiple measurements at different pump speeds. Further research is needed to determine whether cannula flow velocity measurements provide incremental diagnostic or prognostic value in this setting. In the Ramp study, 53% of patients with suspected pump thrombosis required device removal, similar to the 50% in our study. Of those patients who did not require device removal in the Ramp study (4), pump speed ramp studies were used to determine which received intensified anticoagulation and which were monitored for IVH resolution on their pre-existing anticoagulation regimen. In our study, device removal was recommended in the setting of clinical or hemodynamic instability or worsening end-organ dysfunction (such as renal failure secondary to IVH), and all patients who did not require urgent surgery received intensified anticoagulation. The finding of worse cannula Doppler flow velocity profiles in patients presenting with acute HF and those requiring device removal further suggests these parameters may be useful for guiding management in this setting, although larger studies are needed to confirm this.

Study limitations. This was a single-center, retrospective, observational study, and so the presence of bias cannot be excluded. The limited number of patients presenting with IVH may have resulted in some potentially important echocardiographic associations not reaching statistical significance. Validation of these results by a larger multicenter study is warranted. This same limitation prevented

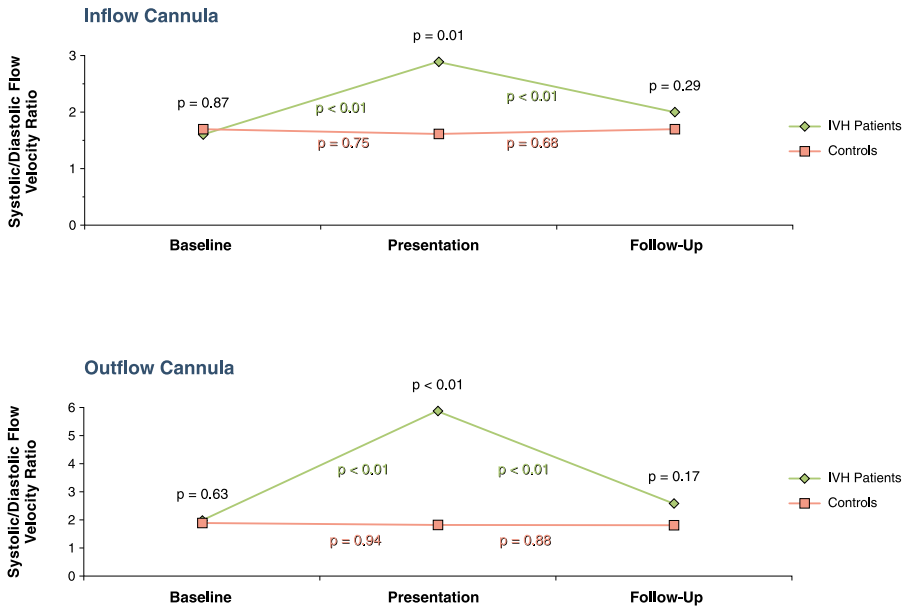

Figure 3. Serial LVAD Inflow and Outflow Cannula S/D Flow Velocity Ratios in IVH Patients and Stable LVAD Control Patients

Comparison of serial systolic/diastolic (S/D) Doppler flow velocity ratios from the inflow **(top)** and outflow **(bottom)** cannulas in LVAD patients with IVH due to suspected pump thrombosis **(green)** and stable LVAD control patients **(pink)** at baseline, at presentation, and in follow-up. p values above the curves **(black)** compare values between IVH and control patients, whereas p values below the curves compare serial measurements at different time points for IVH **(green)** and control **(pink)** patients.

performance of multivariable analysis to determine which echocardiographic variables were independently associated with IVH due to suspected pump thrombosis. Thus, although both the cannula diastolic velocity and S/D velocity ratio were significantly associated with IVH due to suspected pump thrombosis, it remains uncertain whether calculation of the S/D ratio adds incremental value to measurement of cannula velocities alone in this setting. Because the S/D velocity ratio reflects the relative contribution of both the device and the native LV to flow through the pump, we hypothesize that this ratio may be a better measure of the global hemodynamic impact of device dysfunction secondary to pump thrombosis, particularly for patients presenting with acute HF. Although our study demonstrated that IVH patients presenting with acute HF had more deranged echocardiographic findings and worse clinical outcomes than those without HF, it lacked the statistical power to directly determine which echocardiographic variables were associated with clinical outcome. Though highly feasible in our study, cannula Doppler flow velocities may be technically challenging to accurately measure in some LVAD patients. The use of off-axis imaging and the reporting of optimal transthoracic acoustic windows for measuring these parameters at our laboratory aided their feasibility in this study. Technically difficult imaging in some LVAD patients may be a barrier to utilizing these parameters for less experienced echocardiography laboratories. We did not evaluate clinical or biochemical markers associated with pump thrombosis, which were beyond the scope of our study and have been previously well described (4,16). Further studies incorporating clinical, biochemical, and echocardiographic variables would be useful for developing a risk prediction model for LVAD patients presenting with IVH. Our study included only HeartMate II (Thoratec Corporation) patients, and echocardiographic findings in patients with IVH due to suspected device thrombosis of other LVAD models may be different. Lastly, device thrombus was confirmed by inspection in only one-half of the patients in this study.

CONCLUSIONS

HeartMate II (Thoratec Corporation) LVAD patients presenting with IVH due to suspected pump thrombosis have distinct echocardiographic findings that can be used to detect the presence of

device dysfunction. Reduced cannula diastolic Doppler flow velocity and the resultant increased S/D flow velocity ratio were the most important echocardiographic abnormalities found in this setting, and reflect reduced device contribution to pump flow. These findings can aid in the noninvasive assessment and possibly help guide management of LVAD patients with device dysfunction caused by suspected pump thrombosis.

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Key Words: echocardiography ■ intravascular hemolysis ■ left ventricular assist device ■ pump thrombosis.

▶ APPENDIX

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