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Echocardiographic Ramp Test for Continuous-Flow Left Ventricular Assist Devices

Do Loading Conditions Matter?

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ABSTRACT

OBJECTIVES This study investigated whether continuous AI and/or elevated mean arterial pressure (MAP) were associated with false positive results for flow obstruction in echocardiographic ramp speed tests in patients with a continuous-flow left ventricular assist device.

BACKGROUND Failure to reduce the left ventricular end-diastolic diameter (LVEDD) with increasing device speeds in a ramp test is predictive of pump obstruction. Aortic insufficiency (AI) or increased MAP can diminish the ability to unload the left ventricle.

METHODS LVEDD was plotted against device speed, and a linear function slope was calculated. A flat LVEDD slope (≥–0.16) was considered abnormal (suggestive of obstruction). Ramp test results were compared in patients with or without either AI or increased MAP at baseline speed, and receiver-operator characteristic (ROC) curves were constructed for predictors of device obstruction. Device thrombosis was confirmed by direct visualization of clot at explantation or on inspection by the manufacturer.

RESULTS Of 78 ramp tests (55 patients), 36 were abnormal (18 true positive, 18 false positive), and 42 were normal (37 true negative, 5 false negative). In patients with AI, LVEDD slope was –0.14 ± 0.17, which was consistent with device obstruction (vs. –0.25 ± 0.11 in patients without AI; $p < 0.001$), despite no difference in mean lactate dehydrogenase concentration between the 2 groups (1,301 ± 1,651 U/l vs. 1,354 ± 1,365 U/l; $p = 0.91$). Area under the ROC curve (AUC) for LVEDD slope was 0.76 and improved to 0.88 after removal of patients with AI from the study. LVEDD slope in patients with MAP ≥85 mm Hg was similar to that for device obstruction (–0.18 ± 0.07) and was abnormal in 6 of the 12 ramp tests performed. Combining LVEDD slope with lactate dehydrogenase concentration increased the AUC to 0.96 as an indicator of device obstruction.

CONCLUSIONS Abnormal loading conditions due to AI or elevated MAP may result in false positive ramp tests.
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Continuous-flow (CF) left ventricular assist devices (LVADs) provide circulatory support and improve survival, functional capacity, and quality of life in patients with advanced heart failure who are refractory to medical therapy (1). Thromboembolic events are feared complications after implantation of CF-LVADs and are associated with a high degree of mortality and morbidity (2,3). Compared with the initial experience, an increase in the incidence of device thrombosis has recently

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ABBREVIATIONS AND ACRONYMS

AI = aortic insufficiency

AUC = area under the curve

CF = continuous-flow

LDH = lactate dehydrogenase

LVAD = left ventricular assist device

LVEDD = left ventricular end-diastolic diameter

MAP = mean arterial pressure

PI = pulsatility index

ROC = receiver-operator characteristic

been reported in patients who have received the HeartMate II LVAD (Thoratec, Pleasanton, California) (3).

Device thrombosis is clinically suspected in the presence of hemolysis, elevated lactate dehydrogenase (LDH), worsening heart failure, and/or device malfunction (power spike, low-flow alarms). However, diagnosis can be challenging. Echocardiography plays an important role in the evaluation of such patients. Ramp studies, in which left ventricular end-diastolic diameter (LVEDD) is recorded using echocardiography at increasing LVAD speeds, can be used not only to optimize device speed, but also to evaluate potential device obstruction (4,5). Under optimal loading conditions and with no obstruction to flow, an inverse relationship between LVAD speed and LVEDD should be observed. Uriel et al. (4) recently described a standardized protocol for ramp studies in which results were plotted against speed, and linear function slopes were calculated for each parameter. In a prospective cohort of 17 patients in whom device thrombosis was clinically suspected, failure to reduce LVEDD with increased LVAD speed (LVEDD slope ≥−0.16) was strongly associated with significant obstruction to flow (4).

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Currently, ramp tests are used clinically to rule out device obstruction when the LVEDD slope is <−0.16. However, ramp tests are not perfectly predictive of device thrombosis, and we sought to investigate the conditions under which the test may not perform well. One complication of CF-LVADs that can affect ramp test outcome is the development of de novo continuous aortic insufficiency (AI), which imposes an increase in both pre-load and afterload throughout the cardiac cycle (6). As described in previous case reports, this potentially leads to an inability to decompress the left ventricle, with ensuing recurrent heart failure or hemolysis, which results in a scenario mimicking device thrombosis (7,8). Furthermore, because the flow generated by CF-LVADs varies with the pressure differential across the pump, output depends on both pre-load and afterload; thus, blood pressure control is essential (9,10).

Abnormal loading conditions due to either AI or increased mean arterial pressure (MAP) can result in diminished ability to unload the left ventricle. Therefore, the presence of such conditions during a ramp study in patients with a LVAD could result in an abnormal LVEDD slope (≥−0.16) that might be falsely interpreted as suggesting device obstruction (8). Conversely, a clot may be present, but depending on the degree of obstruction and location, the LVEDD slope may be <−0.16, which could be falsely interpreted as a negative result and suggests no obstruction to flow.

In the present study, we sought to address this question in a larger cohort of patients. We hypothesized that the presence of continuous AI or increased MAP (≥85 mm Hg) at baseline speed without clinical evidence of device obstruction was associated with an abnormal LVEDD slope despite the absence of flow obstruction. In addition, we explored the sensitivity and specificity of various cutoff points for LVEDD slope in the evaluation of ramp test results and the usefulness of including LDH and plasma free hemoglobin in the evaluation of potential device thrombosis.

METHODS

PATIENTS. Data from all patients undergoing ramp tests at the University of Minnesota are collected in a prospectively designed database. We reviewed results of ramp tests performed in patients with an implanted CF-LVAD from June 1, 2012 through February 28, 2014, and the last follow-up took place in May 2014. The study was approved by the University of Minnesota Institutional Review Board, and the requirement for individual consent was waived.

PROCEDURES. All patients underwent implantation of the HeartMate II LVAD device. A ramp study with a standardized protocol, as described by Uriel et al. (4), was performed as a routine study in new implants once medical therapy was optimized. Ramp studies were also performed for evaluation of patients who had clinically suspected device thrombosis or recurrent heart failure. Device thrombosis was suspected clinically, and a ramp test was performed when patients presented with: 1) asymptomatic sustained power elevation 14 days after device implantation, which was defined as power ≥10 W or power >2 W above baseline for >24 h; 2) elevated LDH concentration ≥2 times the upper limit of normal for our laboratory (cutoff = 2 × 750 U/l = 1,500 U/l); 3) clinical signs of hemolysis; or 4) symptoms of heart failure in the absence of other causes (5). Device thrombosis was confirmed by direct visualization of the clot at the time of explantation or by manufacturer analysis of the explanted device.

RAMP TEST PROTOCOL. Transthoracic echocardiography was performed using an IE33 ultrasound system (Philips Medical Systems, Andover, Massachusetts). We performed the ramp test as described by Uriel et al. (4). Patients were first assessed for adequate anticoagulation, which was defined as an international

normalized ratio >1.8, and for evidence of intraventricular or aortic root thrombosis (detection of thrombosis by transthoracic echocardiography would preclude proceeding with the ramp study). If these safety conditions were met, the LVAD speed was lowered to a baseline level of 8,000 rpm. The device speed was then increased by 400 rpm at 2-min intervals, with acquisition of all the echocardiographic and device parameters at each step (4).

ASSESSMENTS. Comprehensive clinical, laboratory, device, and echocardiographic data were collected at each surveillance encounter. Baseline LDH concentration was established 1 month after implantation; repeat testing was performed at each encounter and served as 1 of the criteria for the decision to do a ramp test (a value of ≥1,500 U/l was a trigger for ramp testing). LDH and plasma free hemoglobin were determined simultaneously in all patients referred for ramp testing. Device data collected during the ramp study included pump speed (rotations per minute), power, flow, and the pulsatility index (PI). Echocardiographic measurements included LVEDD and left ventricular end-systolic diameter measured from the parasternal long-axis view and the end-diastolic interventricular septum position (neutral, or shifted leftward or rightward). Aortic valve opening was assessed using the M-mode technique over the aortic valve in the parasternal long-axis view. At least 10 consecutive cardiac cycles were reviewed, and the frequency of aortic valve opening was recorded as closed, opened intermittently, or opened every cardiac cycle. Valvular regurgitation was qualitatively assessed using color-flow Doppler imaging (11) and graded according to American Society of Echocardiography guidelines (6,12) as follows: normal and/or trivial = 0; mild = 2; moderate = 3; and severe = 4. The presence of AI was assessed at each step of the ramp study. AI was deemed significant if continuous aortic regurgitation was considered to be equal to or greater than mild-to-moderate in severity (6,8,12,13). MAP was measured at baseline speed before ramp testing and with each speed change. The hypertensive response was defined as a MAP ≥85 mm Hg at baseline speed measured before the ramp test (14,15).

FOLLOW-UP. Patients were followed after the ramp test for confirmation of device thrombosis at the time of device exchange, urgent transplantation, or at time of death. All patients with suspected hemolysis had their devices inspected at these time points. Patients were followed for a minimum of 3 months post-ramp test, and no patients were lost to follow-up.

STATISTICAL ANALYSIS. Data were recorded using Excel 2011 (Microsoft, Redmond, Washington) and analyzed using Excel or Stata software (version 13, StataCorp, College Station, Texas). For each ramp test, LVEDD, PI, and power were plotted against device speed, and linear function slopes were calculated. A flat LVEDD slope (≥-0.16) was categorized as abnormal (suggestive of flow obstruction) (4). Continuous variables were presented as mean ± SD or median (interquartile range), and the significance of differences was tested using either *t*-tests or the Wilcoxon rank sum test. Categorical variables were reported as numbers and percentages and tested using chi-square or Fisher's exact tests. Receiver-operator characteristic (ROC) curves were constructed for LVEDD slope, LDH concentration, plasma free hemoglobin, and a combination of LVEDD slope and LDH concentration as predictors of device obstruction, and the area under the curve (AUC) was calculated. The Youden index was used to calculate optimal cutoff points for the predictors LDH concentration and LVEDD slope. Values of $p < 0.05$ were considered significant.

TABLE 1 Baseline Characteristics and Outcomes in Relation to Device Thrombosis

Characteristics	No Thrombus (n = 42)	Confirmed Thrombus (n = 13)	p Value
Age (yrs)	57.5 ± 14.4	56.5 ± 18.2	0.84
Male	35 (83.3)	12 (92.3)	0.66
CAD	26 (61.9)	9 (69.2)	0.75
Diabetes	14 (33.3)	7 (53.9)	0.18
Hypertension	16 (38.1)	5 (38.5)	0.98
COPD	5 (11.9)	3 (23.1)	0.38
Former tobacco use	19 (45.2)	5 (38.5)	0.62
Current tobacco use	11 (26.2)	1 (7.7)	0.26
BMI (kg/m^2)	30.3 ± 8.7	30.2 ± 8.0	0.97
CABG	11 (26.2)	5 (38.5)	0.40
PCI	12 (28.6)	3 (23.1)	>0.99
Chronic kidney disease	13 (31.0)	3 (23.1)	0.73
INTERMACS score			0.43
1	4 (9.5)	2 (15.4)	
2	7 (17.1)	1 (7.7)	
3	8 (19)	1 (7.7)	
4	10 (23.8)	3 (23.1)	
5	7 (16.7)	6 (46.2)	
6	5 (12.0)	0 (0)	
7	1 (2.4)	0 (0)	
Death	7 (16.7)	2 (15.4)	0.096
Transplant	4 (9.5)	2 (15.4)	0.079
Device exchange	0 (0)	9 (69.2)	<0.001

Values are mean ± SD or n (%).

BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; PCI = percutaneous coronary intervention.

RESULTS

PATIENT DEMOGRAPHIC AND CLINICAL CHARACTERISTICS. A total of 78 ramp tests were performed in 55 patients during the study period. The overall mean age was 57.4 ± 15.8 years, with a predominately male cohort (47 men and 8 women). The patients' demographic and clinical characteristics and outcome variables are shown in Table 1 according to thrombosis status (confirmed by direct visualization or manufacturer analysis). All patients in the thrombosis group had visual confirmation of device obstruction. The median time to first hemolysis event in the thrombus group was 101 days (range 45 to 1,113 days). No significant differences were observed between patients with and without thrombosis, except that the device was exchanged in 9 (69.2%) of the 13 patients with thrombosis versus none of the patients without thrombosis ($p < 0.001$). In the device thrombosis group, 2 patients underwent device explantation at the time of urgent heart transplantation, and 1 patient treated with thrombolytics died secondary to an intracranial hemorrhage post-infusion.

RAMP TEST PERFORMANCE. Of the 78 ramp tests, 15 (19.2%) were performed for evaluation of heart failure and device optimization, 34 (43.6%) were done for evaluation of possible device thrombosis, and 29 (37.2%) were routine tests performed once medical therapy was optimized. Ramp test results are reported in Table 2 according to thrombosis status. The LVEDD slope was significantly less steep when thrombosis was present ($p = 0.008$). Furthermore, LDH concentrations were significantly higher in the confirmed thrombosis group than in the non-thrombosis group when measured at the time of referral for ramp testing ($p < 0.001$).

TABLE 2 Ramp Test Results in Relation to Device Thrombosis

Characteristics	No Thrombus (n = 42)	Confirmed Thrombus (n = 13)	p Value
Number of ramp tests	55	23	
LVEDD slope	−0.22 ± 0.12	−0.13 ± 0.13	0.008
PI slope	−0.33 ± 0.15	−0.30 ± 0.23	0.40
Power slope	0.64 ± 0.17	0.63 ± 0.12	0.92
MAP slope	1.4 ± 2.0	1.0 ± 3.0	0.96
Speed for complete AV closure (rpm)	9,200 (8,800-9,600)	9,600 (8,600-10,000)	0.34
LDH at baseline (U/l)	782 ± 191	824 ± 155	0.36
LDH at ramp test (U/l)	1,058 ± 996	3,617 ± 1,615	<0.001
LDH 3 × ULN	10 (18.2)	19 (82.6)	<0.001
Plasma free HGB (mg/dl)	17.4 ± 8.6	36.0 ± 49	0.02
Plasma free HGB >40 mg/dl	5 (9.1)	6 (26.1)	0.049
Days with VAD	478.5 (44-1692)	277 (47-1147)	0.18

Values are mean ± SD, median (interquartile range), or n (%). Data are based on the total number of ramp tests. LDH baseline was measured 1 month after implantation.

AV = aortic valve; HGB = hemoglobin; LDH = lactate dehydrogenase; LVEDD = left ventricular end-diastolic dimension; MAP = mean arterial pressure; PI = pulsatility index; ULN = upper limit of normal; VAD = ventricular assist device.

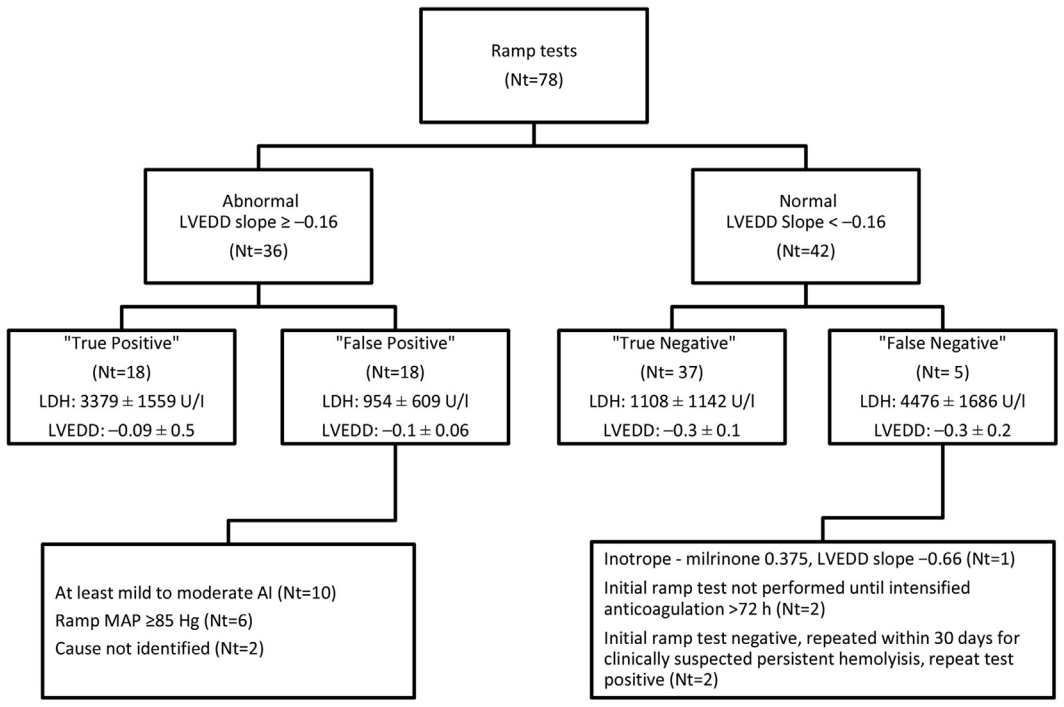
The classification of the results of all ramp tests based on LVEDD slope is shown in Figure 1. Of the 78 tests, 36 (46%) had an LVEDD slope ≥−0.16 and were categorized as abnormal (suggestive of flow obstruction = positive). Of the 36 abnormal ramp tests, 18 tests (in 12 patients) correctly indicated thrombosis as shown by direct clot visualization at the time of explantation, and the results were classified as true positive. For 18 tests (in 15 patients), despite the abnormal LVEDD slope, no thrombosis was suspected based on ongoing CF-LVAD support, without evidence of device obstruction or hemolysis, and with no requirement for urgent device exchange or heart transplantation. Therefore, these results were classified as false positive.

Of the 18 false positive ramp tests, 10 tests were performed in 7 patients who were found to have significant AI; 6 tests were in 6 patients who started with a MAP ≥85 mm Hg that remained consistently >85 mm Hg throughout the study; 1 test was in a patient with high cardiac output heart failure in the setting of bacteremia; and, for 1 test, no cause for the abnormal result could be identified. There was no significant difference in mean LVEDD slope between the false positive tests (−0.10 ± 0.06) and the true positive tests (−0.09 ± 0.50; $p = 0.45$). No significant differences in power, PI, and MAP at baseline were observed. However, mean LDH was significantly lower in false positive ramp tests (954 ± 609 U/l) than in true positive tests (3,379 ± 1,559 U/l; $p < 0.001$) (Figure 1).

During a mean follow-up of 278.8 ± 166.9 days in the false positive group, 3 patients underwent nonurgent heart transplantation; 1 death occurred from an intracranial hemorrhage in the setting of a supratherapeutic international normalized ratio of 9, and no device exchanges were performed.

A total of 37 tests with normal LVEDD slopes were shown to correctly indicate the absence of device obstruction and were categorized as true negative (Figure 1). In 4 patients, 5 tests failed to identify the presence of thrombosis and/or hemolysis and were classified as false negative. The first patient received milrinone for biventricular failure. The second patient had 2 false negative ramp tests: 1 was performed after 72 h of anticoagulation with high-intensity intravenous unfractionated heparin; and a second ramp test, which was performed 48 h before urgent device exchange because of hemodynamic compromise, remained negative. In another 2 patients, ramp tests performed for hemolysis were initially

FIGURE 1 Classification of Ramp Test Results



LDH = lactate dehydrogenase; LVEDD = left ventricular end-diastolic diameter; MAP = mean arterial pressure; Nt = number of ramp tests.

negative, but subsequent tests for recurrent ongoing hemolysis, increasing LDH, and signs of heart failure were positive.

AORTIC INSUFFICIENCY. Results of ramp tests in patients with significant (at least mild-to-moderate) AI were compared with those in patients without significant AI. All 18 true positive ramp tests were excluded in this analysis (1 was in a patient with thrombosis and AI, and 17 were in patients with thrombosis without AI). Thus, a total of 13 ramp tests performed in 10 AI patients were compared with 47 ramp tests performed in 33 patients without significant AI. As shown in Table 3, the mean LVEDD slope was significantly flatter when significant AI was present than when it was not ($p < 0.001$), which indicated that tests in AI patients had an LVEDD slope consistent with device obstruction, despite no difference in LDH concentration between the 2 groups. Of the 13 ramp tests in patients with AI, 10 tests (77%) showed an abnormal LVEDD slope (≥−0.16). None of these patients had clinical suspicion of LVAD obstruction or hemolysis. There were no significant differences between patients with and those without AI in PI slope, power slope, MAP at baseline, or LDH concentration (Table 3). Furthermore, there were no differences in ramp test parameters between the 13 tests in patients with AI and the 18 tests with true positive results. However, LDH concentrations were significantly lower for tests in AI patients (1,301 ± 1,651 U/l) than for true positive tests (3,379 ± 1,559 U/l; $p = 0.001$).

MEAN ARTERIAL PRESSURE. To investigate the association between hypertension and LVEDD slope, we compared test results for patients with hypertension (MAP ≥85 mm Hg) at baseline speed at the time of the ramp test versus results for patients without hypertension (MAP <85 mm Hg). All 18 true positive tests were excluded from the comparison (1 test in a patient with hypertension and 17 tests in patients without hypertension). Thus, a total of 12 ramp tests performed in 12 patients with hypertension were compared with 48 ramp tests performed in 31 patients without hypertension (Table 4). Patients with MAP ≥85 mm Hg had a mean LVEDD slope similar to that reported in device obstruction, whereas patients without hypertension had a steeper mean LVEDD slope; however, the difference was not significant ($p = 0.25$). No significant differences were

TABLE 3 Ramp Test Results in Patients Without or With Aortic Insufficiency

Characteristics	No AI (n = 33)	AI (n = 10)	p Value
Number of ramp tests	47	13	
LVEDD slope	−0.25 ± 0.11	−0.14 ± 0.17	<0.001
PI slope	−0.34 ± 0.17	−0.34 ± 0.12	0.93
Power slope	0.64 ± 0.17	0.63 ± 0.18	0.83
MAP at baseline speed (mm Hg)	80.4 ± 12.6	76.7 ± 6.6	0.42
LDH at ramp test (U/l)	1,354 ± 1,365	1,301 ± 1,651	0.91

Values are mean ± SD. Data are based on the total number of ramp tests.
AI = aortic insufficiency (at least mild-to-moderate); other abbreviations as in Table 2.

observed between patients with and those without hypertension with regard to PI, power slope, or LDH levels at the time of the ramp test. Of the 12 ramp tests performed in patients with baseline MAP ≥85 mm Hg at the time of ramp testing, 6 tests (50%) had an abnormal LVEDD slope (≥−0.16) with no confirmation of hemolysis or device obstruction. The patient with hypertension in the true positive group had high clinical suspicion of device obstruction; when the ramp test was repeated in this patient after MAP was lowered to <85 mm Hg, no change was observed in LVEDD slope, and a clot was confirmed on device explantation. There were no significant differences in ramp test parameters between tests in patients with MAP ≥85 mm Hg and true positive tests, except that mean LDH concentration was 1,188 ± 610 U/l when MAP was ≥85 mm Hg versus 3,379 ± 1,555 U/l for true positive tests (p = 0.001).

PREDICTORS OF DEVICE OBSTRUCTION. An ROC curve constructed for LVEDD slope as a predictor of device obstruction (based on all ramp tests) had an AUC of 0.76 (Figure 2). The cutoff point of −0.16 as reported by Uriel et al. (4) for LVEDD slope had a sensitivity of 78% and specificity of 66%. The optimal cutoff point based on the Youden index was an LVEDD slope of −0.18, with an AUC of 0.73, sensitivity of 87%, and specificity of 60%. When the ROC curve was reanalyzed after removal of tests in patients with significant AI, the AUC improved to 0.88 (Figure 3). When the ROC curve was again reanalyzed after controlling for MAP, the AUC did not change.

When an ROC curve was constructed for LDH concentrations as a predictor of device obstruction (based on all LDH values), the AUC was 0.92 compared with the AUC of 0.76 for LVEDD slope (Figure 2). Using 2.5 times the upper limit of normal (≥875 U/l) as the cutoff point for LDH resulted in a sensitivity of 91% and a specificity of 86%; a cutoff of 2 times the upper limit of normal (≥1,500 U/l) had a sensitivity of 90% and a specificity of 82%. The optimal cutoff point for LDH calculated with the Youden index was LDH >2,108 U/l (approximately 2.8 times the upper limit of normal), with a sensitivity of 0.87 and a specificity of 0.93 (AUC: 0.90).

When an ROC curve was constructed for plasma free hemoglobin as an indicator of device obstruction (based on all values), the AUC was 0.62. A cutoff of >25 mg/dl had a sensitivity of 35% and a specificity of 95%. The combination of plasma free hemoglobin and LDH as an indicator of device obstruction had an AUC of 0.92.

When an ROC curve was constructed for the combination of LDH concentration and LVEDD slope as an indicator of device obstruction (based on all values), the AUC was 0.96 (Figure 4).

TABLE 4 Ramp Test Results in Relation to Hypertension

Characteristics	No HTN Response (MAP <85 mm Hg) (n = 31)	HTN Response (MAP ≥85 mm Hg) (n = 12)	p Value
Number of ramp tests	48	12	
LVEDD slope	−0.23 ± 0.14	−0.18 ± 0.07	0.25
PI slope	−0.34 ± 0.17	−0.35 ± 0.13	0.82
Power slope	0.63 ± 0.18	0.67 ± 0.14	0.52
MAP at baseline speed (mm Hg)	75.0 ± 7.6	95.2 ± 10.1	<0.001
LDH at ramp test (U/l)	1,381 ± 1,557	1,188 ± 610	0.15

Values are mean ± SD. Data are based on the total number of ramp tests. All 18 true positive ramp tests were excluded.
HTN = hypertension (MAP ≥85 mm Hg at baseline speed before the ramp test); other abbreviations as in Table 2.

DISCUSSION

In this study, we corroborated the findings by Uriel et al. (4) that the ramp test is a useful tool for evaluating suspected device obstruction in patients with a CF-LVAD. However, conditions that result in ineffective decompression of the left ventricle, such as continuous AI, uncontrolled hypertension, inotropic therapy, and sepsis, may affect the relationship between device speed and changes in the LVEDD. Our data provided evidence that the presence of AI or hypertension can blunt changes in the LVEDD with increasing speed in patients with CF-LVADs, even when no obstruction to flow is present, thus resulting in false positive ramp test results. These data provide an important insight into the interpretation of ramp studies under different loading conditions.

The standardized ramp study protocol described by Uriel et al. (4) was accurate for the detection of pump thrombosis when used in combination with LDH levels in 17 patients with suspected device obstruction. All 8 patients whose devices were explanted

after an abnormal ramp study (LVEDD slope ≥−0.16) had either a thrombus in the pump or disconnection of the outflow graft bend relief that was responsible for stabilizing the proximal outflow graft. In that study, the mean MAP was 85.3 ± 9.7 mm Hg; the presence of AI was not reported (4).

In our study, the LVEDD slope had only "fair" discriminative power (AUC: 0.76) for the prediction of LVAD obstruction based on ramp test results from our entire patient cohort. However, when patients with more than mild-to-moderate AI were excluded, discriminative power improved (AUC: 0.88). Controlling for MAP did not have a significant effect on the AUC. More importantly, when the ROC curve was calculated based on the LDH concentration, which was determined at the time of ramp testing combined with LVEDD slope in our entire cohort, the AUC improved to 0.96. The 2 tests in combination were the best indicators for device obstruction in our cohort.

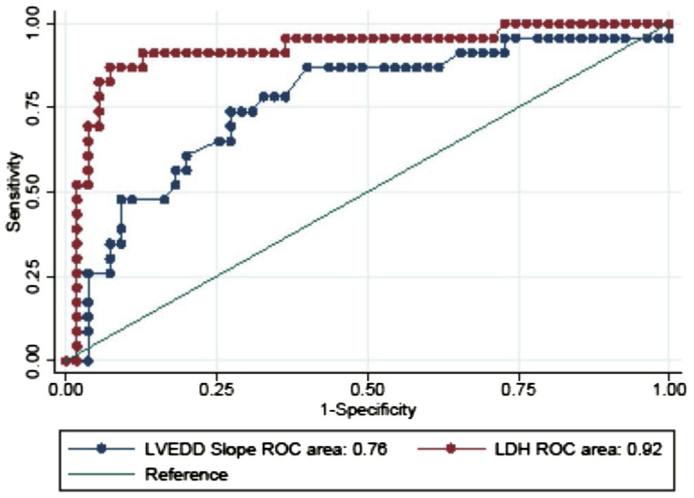
Analysis of the false negative tests illustrates a key point for the consideration of ramp testing. Because we implemented routine surveillance of LDH with a trigger of LDH 2 times the upper limit of normal for ramp test referral, we showed that flow obstruction may not exist in the early phase of clot formation. Thrombus formation appears to be layered, with progressive layering resulting in obstruction and pump malfunction. Thus, in the early phase of clot formation or even thrombus formation on the inflow stator, there may not be obstruction to flow, and the ramp test may be negative despite ongoing hemolysis and the need for aggressive anticoagulation.

Tests in patients with significant (at least mild-to-moderate), continuous AI had an average LVEDD slope (−0.14) during the ramp study after exclusion of all true positive tests, and the LVEDD slope was abnormal in 77% of the ramp tests performed. We did not find any ramp test characteristics that distinguished AI from true obstruction to flow; in these patients, LDH was the best indicator for device obstruction. To date, we have followed this group of AI patients for >6 months from the time of the ramp study; there has been no evidence of device obstruction or hemolysis, except in 1 patient. This patient had hemodynamic instability with a high clinical suspicion of LVAD thrombosis. Urgent device exchange was performed, and the presence of thrombus was confirmed on both the inflow stator and outflow bearings, with >60% obstruction to flow.

In CF-LVADs, pump output is regulated by pre-load and afterload sensitivity. A study by Salamonsen et al. (9) presented data that showed that pre-load sensitivity in rotary blood pumps was about twice as low as that of the human heart, and afterload sensitivity was up to 3 times as high. Axial and centrifugal pumps showed similar relationships between pressure and flow because the pressure differential increases as the pump output decreases.

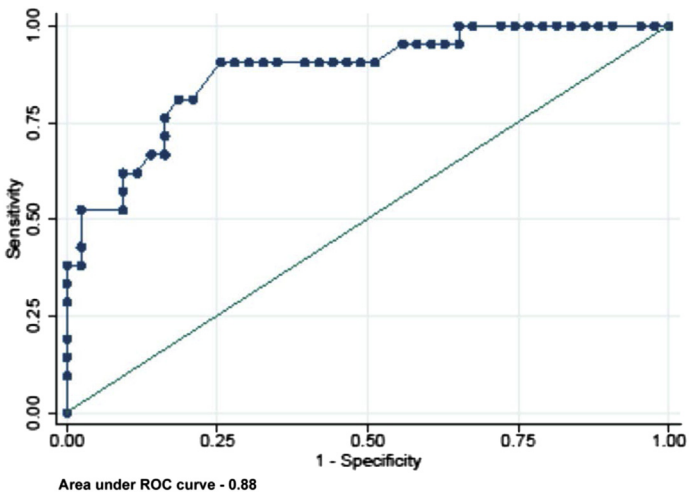
One characteristic of AI in patients with CF-LVADs is that it can become continuous throughout the cardiac cycle and impose an increase in both pre-load and afterload of the left ventricle. In the setting of a

FIGURE 2 ROC Curve for LVEDD Slope versus LDH Concentration: All Ramp Tests (78 Tests in 55 Patients)



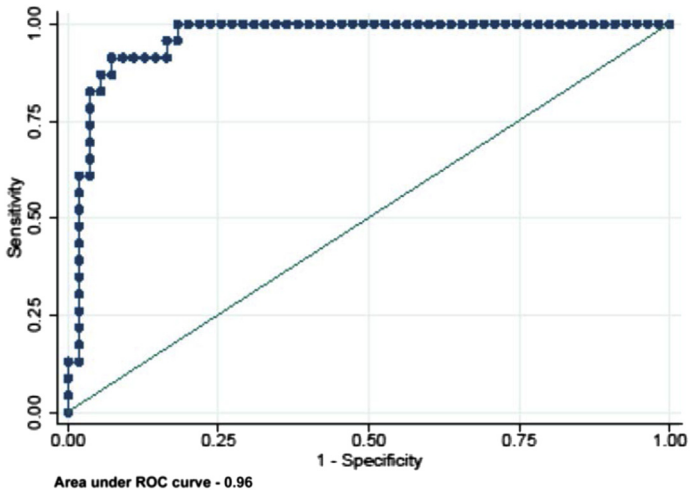
ROC = receiver operator characteristic; other abbreviations as in Figure 1.

FIGURE 3 ROC Curve for LVEDD Slope for Ramp Tests Excluding Aortic Insufficiency



Abbreviations as in Figures 1 and 2.

FIGURE 4 ROC Curves Combining LVEDD Slope and LDH Concentration for All Ramp Tests



Abbreviations as in Figures 1 and 2.

well-functioning LVAD, the transaortic valve regurgitant flow rate is determined by systemic MAP, intracavitary left ventricular pressure, and impedance of the aortic valve to retrograde flow. This can lead to decreased LVAD forward output, which is caused by recirculation of regurgitant blood from the outflow cannula back into the left ventricular inflow cannula (6,16–18). This may explain our finding of a flat LVEDD slope during the ramp study without device obstruction. The effect of AI on the hemodynamic response in patients with a CF-LVAD was measured in a mock loop over a range of pump speeds and levels of native cardiac function (19). That study showed that wasteful recirculation caused by AI substantially increased the pump work and decreased systemic perfusion, in particular during series flow conditions coupled with higher LVAD speeds.

Quantification of AI in patients with LVADs is graded according to American Society of Echocardiography criteria based on patients with native aortic regurgitation. It is not clear whether the same criteria should be applied to LVAD patients with continuous AI. In the present study, the ramp test identified a subgroup of patients with AI without effective decompression of the left ventricle by the LVAD. Further studies are required to assess whether an abnormal LVEDD slope predicts worse outcomes in patients with AI. Only 1 of our 10 patients with AI had clinical suspicion of device obstruction. Thus, we could not determine the best LVEDD slope to predict LVAD thrombosis in the context of AI.

Uncontrolled MAP has been also proposed as a mechanism of lack of effective unloading of the left ventricle with CF-LVADs (10). Guidelines support maintaining a MAP ≤80 mm Hg in patients with a nonpulsatile mechanical circulatory support system. As part of our current ramp protocol, MAP is now titrated to <85 mm Hg in all patients. However, in the present study, 12 tests were performed in patients with uncontrolled MAP at the time of the ramp test (defined as MAP ≥85 mm Hg at baseline speed). Although the mean LVEDD slope in these patients was not significantly different from patients without hypertension, 6 tests (50%) had an abnormal LVEDD slope despite the absence of hemolysis or device obstruction. In 2 patients, controlling MAP achieved normalization of the LVEDD slope when the ramp test was repeated. In the patient with both uncontrolled hypertension and confirmed device thrombosis, the ramp test was still abnormal when it was repeated after aggressive afterload reduction and normalization of MAP. These data suggest that, to avoid false positive results, strict blood pressure control is needed before a ramp study is performed.

The percentage of deaths in our cohort was similar between the no thrombus and the confirmed thrombosis groups. The majority of our patients were managed by either device exchange or urgent cardiac transplantation as the preferred treatment. Medical management at our institution is reserved only for those patients who are not candidates for these therapies. Only 2 patients with thrombosis were managed medically, 1 of whom received thrombolytics. Starling et al. (3) reported that mortality at 6 months among patients treated with device replacement or transplantation was similar to that among patients who did not have device thrombosis, whereas medical management was associated with a 48.2% mortality. Timing of surgical intervention depends on end organ function and hemodynamic stability; we do attempt initial medical stabilization with high-intensity intravenous unfractionated heparin and antiplatelet therapy before definitive treatment.

STUDY LIMITATIONS. This was a single-center analysis of data from a relatively small cohort collected in a prospectively designed database, although it was one of the largest cohorts with long-term follow-up reported to date. We could not exclude bias regarding echocardiographic image acquisition or interpretation of the severity of AI. As with most single-center LVAD analyses, our study power was limited. Validation of these results by a larger multicenter study is warranted. Our study only included patients

with the Heart Mate II, and echocardiographic findings in patients with other LVAD models might be different.

CONCLUSIONS

The ramp test is useful for detection of CF-LVAD device obstruction. However, in the presence of abnormal loading conditions, such as that in patients with AI or hypertension, increasing pump speed may not lead to effective decompression of the left ventricle, and the LVEDD slope may be abnormal, even in the absence of device obstruction. Longitudinal studies are required to investigate whether abnormal ramp test results in such patients predict negative outcomes.

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