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Development of a Novel Echocardiography Ramp Test for Speed Optimization and Diagnosis of Device Thrombosis in Continuous-Flow Left Ventricular Assist Devices

The Columbia Ramp Study

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Objectives This study sought to develop a novel approach to optimizing continuous-flow left ventricular assist device (CF-LVAD) function and diagnosing device malfunctions.

Background In CF-LVAD patients, the dynamic interaction of device speed, left and right ventricular decompression, and valve function can be assessed during an echocardiography-monitored speed ramp test.

Methods We devised a unique ramp test protocol to be routinely used at the time of discharge for speed optimization and/or if device malfunction was suspected. The patient's left ventricular end-diastolic dimension, frequency of aortic valve opening, valvular insufficiency, blood pressure, and CF-LVAD parameters were recorded in increments of 400 rpm from 8,000 rpm to 12,000 rpm. The results of the speed designations were plotted, and linear function slopes for left ventricular end-diastolic dimension, pulsatility index, and power were calculated.

Results Fifty-two ramp tests for 39 patients were prospectively collected and analyzed. Twenty-eight ramp tests were performed for speed optimization, and speed was changed in 17 (61%) with a mean absolute value adjustment of 424 ± 211 rpm. Seventeen patients had ramp tests performed for suspected device thrombosis, and 10 tests were suspicious for device thrombosis; these patients were then treated with intensified anticoagulation and/or device exchange/emergent transplantation. Device thrombosis was confirmed in 8 of 10 cases at the time of emergent device exchange or transplantation. All patients with device thrombosis, but none of the remaining patients had a left ventricular end-diastolic dimension slope >-0.16.

Conclusions Ramp tests facilitate optimal speed changes and device malfunction detection and may be used to monitor the effects of therapeutic interventions and need for surgical intervention in CF-LVAD patients. (J Am Coll Cardiol 2012;60:1764–75) © 2012 by the American College of Cardiology Foundation

Continuous-flow left ventricular assist devices (CF-LVADs) are an important therapeutic option for patients with advanced congestive heart failure (1–3). LVADs have traditionally been implanted as a bridge to transplantation (2,3), with average support times of 6 to 12 months. However, left ventricular assist devices (LVADs) are increasingly used for the purpose of destination therapy (1), where support duration averages 2 to 4 years and is approaching a decade in individual patients. One-year survival in patients awaiting transplantation while on LVAD support has increased from 55% to 85% (4) and is approaching 80% in destination therapy patients in the most recent U.S. experience (5). Cumulative global experience with the currently U.S. Food and Drug Administration–approved

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HeartMate II device (Thoratec Corporation, Pleasanton, California) exceeds 8,000 patient-years, and it has become clear that management of the patient–device interface (e.g., speed optimization and anticoagulation) is at the epicenter of further improvement possibilities.

Currently, recommendations for device speed adjustment include target measures of mean arterial pressure >65 mm Hg, middle interventricular septum position, and intermittent aortic valve (AV) opening while maintaining no more than mild mitral regurgitation (MR) to ensure appropriate unloading of the left ventricle (6). Optimal speed settings may reduce the frequency of several of the key complications related to long-term LVAD support. The importance of ensuring middle septal position for optimal right ventricular function is now well established (6), but our understanding of speed optimization continues to evolve beyond acute hemodynamic effects. For example, we recently reported the development of de novo aortic insufficiency (AI) in 25% of patients remaining on CF-LVADs for at least 1 year (7). Interestingly, AI occurred in the majority of patients (66%) whose AVs remained closed during support, but rarely (8%) in those whose AV opened regularly; a nearly identical prevalence of AI and association with AV opening has been reported by others (8,9). It is therefore conceivable, although unproven, that proactively maintaining intermittent opening of the AV during support may delay or prevent the development of AI. Intermittent AV opening also results in a more pulsatile flow pattern, and it has been hypothesized that increased pulsatility may attenuate the development of von Willebrand factor deficiency (10).

The dynamic assessment of device speed, left ventricular decompression, and valvular function during an echocardiographically monitored ramp study may not only allow device speed optimization in individual patients, but abnormalities in this interaction may also aid in the diagnosis of device malfunction. Although the use of ramp studies for CF-LVAD management is recommended in the literature, no specific protocol has been reported or endorsed.

In the current study, we aimed to develop a systematic approach to perform and analyze ramp tests to optimize device function and diagnose device malfunctions, specifically device thrombosis, an uncommon but potentially catastrophic complication of CF-LVADs.

Abbreviations and Acronyms

AI = aortic insufficiency
AV = aortic valve
CF-LVAD = continuous-flow left ventricular assist device
LDH = lactate dehydrogenase
LVAD = left ventricular assist device
LVEDD = left ventricular end-diastolic dimension
MR = mitral regurgitation
PI = pulsatility index

Methods

A prospective study of all ramp tests performed at Columbia University Medical Center–New York Presbyterian Hospital from June 1, 2011, until April 5, 2012, was conducted. The Columbia University Institutional Review Board approved this study and all patients signed informed consent.

After devising a standardized ramp test protocol for the HeartMate II (Table 1) in early 2011, ramp tests have been performed at our institution routinely for speed optimization or when device thrombosis is suspected. Protocol for patients supported by the HeartWare device (HeartWare International, Framingham, Massachusetts) is provided in the Online Appendix.

With regard to speed optimization, we followed the current recommendations to ensure middle interventricular septum position, and intermittent AV opening while maintaining no more than mild MR.

Device thrombosis was suspected clinically based on at least 1 the following: 1) transient increases in pump power (power spikes) >14 days after device implantation or gradually increasing power requirements of at least 2 W; 2) lactate dehydrogenase (LDH) level >1,000 U/l or persistently increasing LDH in repeated blood work in conjunction with low haptoglobin and/or high plasma free hemoglobin in the absence of other causes of hemolysis (our

Table 1 Ramp Test Protocol (for HeartMate II)

Speed, rpm	PI	Power	Flow	BP	HR	LVEDD	LVESD	AV Opening	AI	MR	RVSP
8,000											
8,400											
8,800											
9,200											
9,600											
10,000											
10,400											
10,800											
11,200											
11,600											
12,000											

Similar ramp test protocol was developed for the Heartware device.
AI = aortic insufficiency; AV = aortic valve; BP = blood pressure; HR = heart rate; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; PI = pulsatility index; RVSP = right ventricular systolic pressure.

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outpatient LVAD follow-up protocol consists of routine LDH level checks once per month; at Columbia University Medical Center, the upper limit of normal for LDH is 221 IU/l); and the 3) development of left-sided heart failure without apparent other causes such as severe AI.

The final diagnosis of device thrombosis required direct visualization of a clot in the pump on device explantation and/or disassembly by the manufacturer.

Ramp test protocol. First, baseline demographic data as well as surgical history, current medications, and laboratory parameters including anticoagulation, platelet count, and LDH, bilirubin, haptoglobin, and plasma free hemoglobin levels, where applicable, were collected (Fig. 1, Table 1).

Second, baseline parameters were reviewed to ensure safety. 1) Appropriate anticoagulation (international normalized ratio >1.8 or partial thromboplastin time >60 s) was confirmed. If adequate anticoagulation was not demonstrated, a routine ramp test for speed adjustment was postponed until therapeutic anticoagulation was reached. In cases of suspected device thrombosis, heparin 60 U/kg was given intravenously, and the ramp test was subsequently performed. 2) Baseline transthoracic echocardiography was performed; if it revealed an intraventricular or aortic root thrombus, the ramp study was not performed due to the possibility of thrombus dislodgment.

Third, baseline echocardiographic and device parameters (see the following for details) were recorded.

Pulsatility index. Contraction of the left ventricle increases the flow of blood into the pump. The magnitude of these flow pulses is measured by the pump and averaged over a 15-s interval to produce the displayed pulsatility index (PI) value.

Suction events occur when the pump speed is set high enough to cause partial collapse of the left ventricle resulting in obstruction of the inflow cannula by adjacent myocardium. When suction events occur, they automatically reduce the speed to the low speed setting (typically set at 400 to 800 rpm below the fixed speed setting).

Fourth, the LVAD back-up speed was set at 8,000 rpm to allow the actual device speed to be set as low as 8,000 rpm without causing low-flow speed alarms.

Fifth, the patient's device speed was lowered to 8,000 rpm. After 2 min, transthoracic echocardiographic images were obtained, and the following parameters were recorded: left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic diameter, frequency of AV opening, degree of AI, degree of MR, right ventricular systolic pressure, Doppler blood pressure, and heart rate. In addition, the following pump parameters were recorded: power, PI, and flow.

Specifically, transthoracic echocardiographic parameters were measured as follows (Fig. 2). 1) LVEDD and left ventricular end-systolic dimension were measured from the parasternal long-axis view (Fig. 2A). 2) AV opening was assessed using M-mode over the AV in the parasternal long-axis view. At least 10 consecutive cardiac cycles were reviewed, and the frequency of AV opening was recorded as

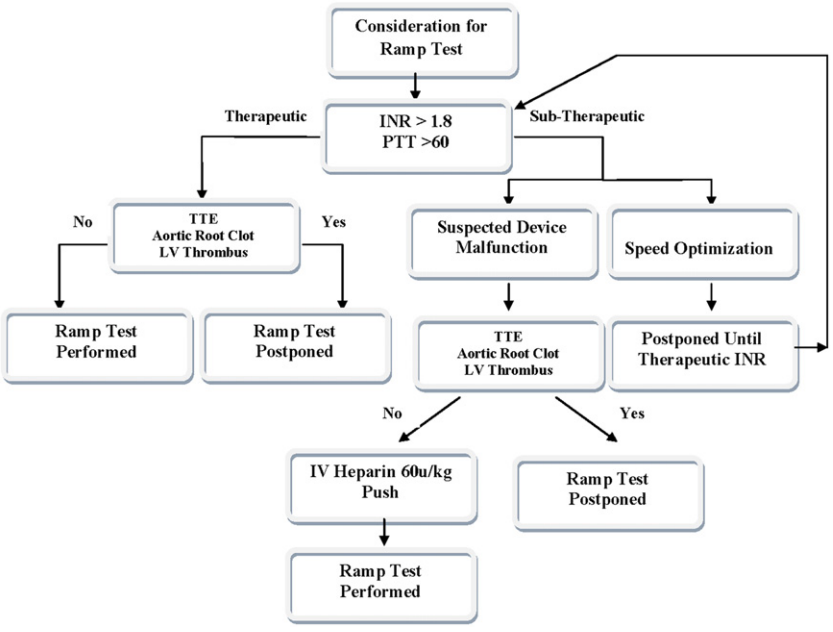

Figure 1 Consideration for the Ramp Test Algorithm

Algorithm for consideration of ramp tests based on anticoagulation studies and presence of intracardiac thrombus. Blood pressure should be below 110 mm Hg by Doppler in order to be eligible to start the ramp test. INR = international normalized ratio; IV = intravenous; LV = left ventricular; PTT = partial thromboplastin time; TTE = transthoracic echocardiography.

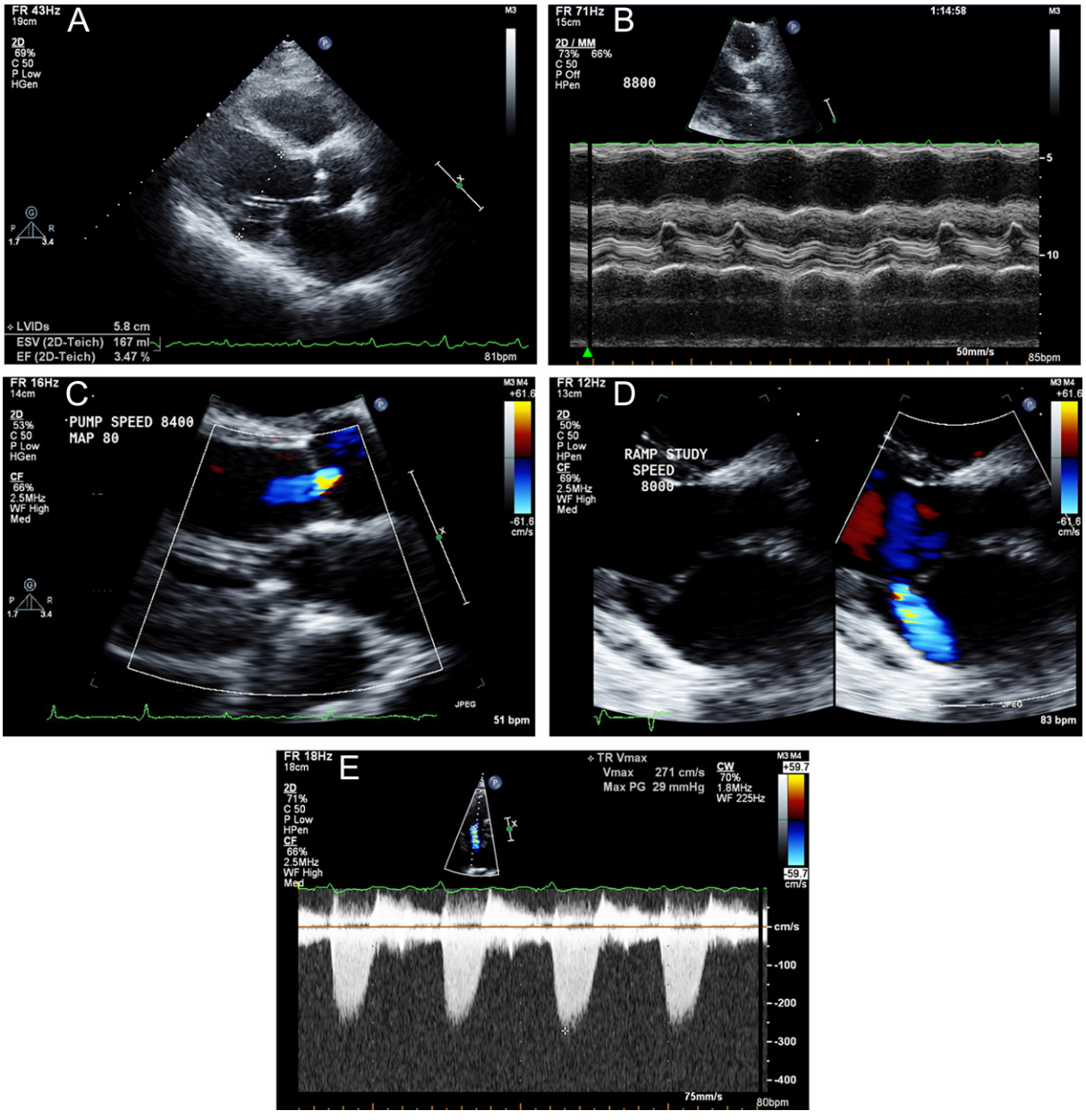

Figure 2 **Images for Obtaining Transthoracic Echocardiography Parameters**

(A) Left ventricular end-diastolic dimension assessment in the parasternal long-axis view. **(B)** Aortic valve opening assessment by M-mode. **(C)** Aortic valve insufficiency assessment by color Doppler imaging. **(D)** Mitral valve insufficiency assessment by color Doppler imaging. **(E)** Right ventricular systolic pressure assessment by Doppler imaging. MAP = mean arterial pressure.

the percentage of cycles with AV opening (Fig. 2B). 3) Visual estimation of the severity of AI and MR was performed in the parasternal long-axis view using the color Doppler imaging technique (Figs. 2C and 2D). For assessment of AI and MR, the degree of regurgitation was graded from 0 to 6 (0 = none; 1 = trace; 2 = mild; 3 = mild to moderate; 4 = moderate; 5 = moderate to severe; 6 = severe). Taking into account that AI during CF-LVAD support is generally both systolic and diastolic, AI was deemed significant if graded 3 (mild to moderate) or greater (7). 4) Right ventricular systolic pressure was estimated from peak tricuspid regurgitant velocity using modified Bernoulli's equation (Fig. 2E).

Next, the device speed was subsequently increased by 400 rpm at 2-min intervals with repeated acquisition of all echocardiographic and device parameters at each speed step. The 400-rpm increments continued from 8,000 to 12,000 rpm. The ramp test was stopped if any suction events

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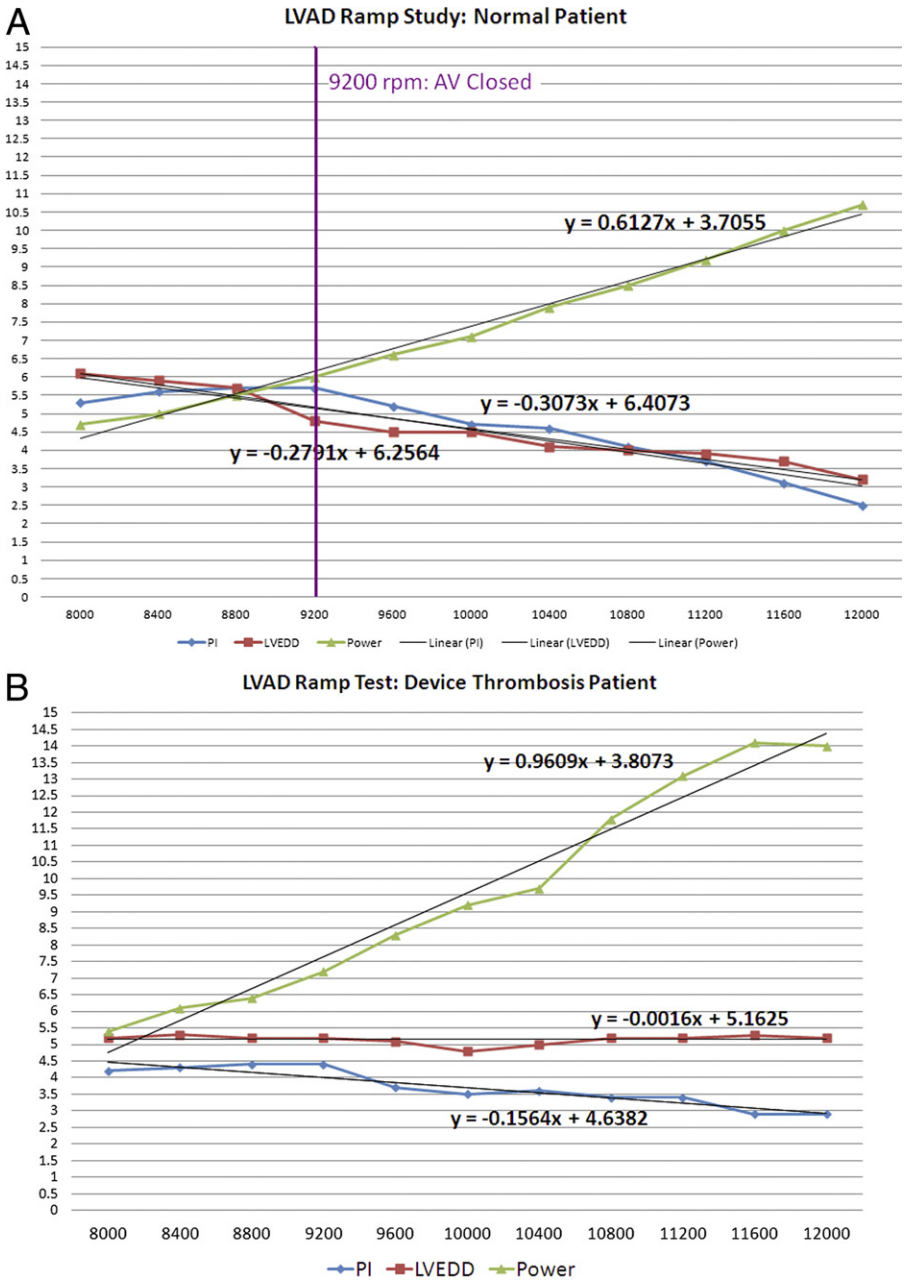

Figure 3 Graphs of Normal Example Versus Device Thrombosis Example of LVEDD, PI, and Power

(A) LVEDD slope, PI slope, and power slope of a patient with normal device function. **(B)** LVEDD slope, PI slope, and power slope of a patient with device thrombosis.
AV = aortic valve; LVAD = left ventricular assistive device; LVEDD = left ventricular end-diastolic dimension; PI = pulsatility index.

occurred and/or if the LVEDD decreased to <3.0 cm. At the test's conclusion, the attending cardiologist reviewed the recordings from the test while at the patient's bedside. Device speed was then set to allow intermittent AV opening while maintaining Doppler blood pressure >65 mm Hg and avoiding more than mild MR.

Finally, the recordings of the ramp test parameter results at the respective 11 speed points were plotted in Excel 2007 software (Microsoft Corp., Redmond, Washington). Linear function slopes for LVEDD, PI, and power were calculated (Fig. 3A) using Excel software.

Statistical analysis. Data were collected using Excel 2007 software. All data were analyzed using R version 2.15.0. Categorical variables were summarized by frequencies and percentages and were analyzed using the Fisher exact test. The Student *t* test for independent samples was used to determine differences in normally distributed data. The Wilcoxon rank sum test was used to determine differences in

Table 2 Baseline Characteristics and Results: Device Thrombosis Patients (n = 8) Versus No Thrombosis Patients (n = 29) Versus All Patients (n = 39)

	Confirmed Thrombosis Patients (n = 8)	No Thrombosis Patients (n = 29)	p Value	All Patients (n = 39*)
Age, yrs	53 ± 20	59 ± 14	0.47	57 ± 14
Male	5 (62)	26 (90)	0.10	33 (85)
Race	2 (25) AA, 6 (75) other	3 (12) AA, 22 (88) other	1.0	6 (15) AA, 33 (85) other
Heart failure etiology, dilated cardiomyopathy	4 (50)	12 (48)	0.70	20 (51)
Hypertension	3 (38)	7 (28)	1.0	13 (33)
Diabetes mellitus	3 (38)	7 (28)	0.66	14 (36)
Former smoker	5 (62)	14 (56)	0.70	21 (54)
IVS, cm	1.0 ± 0.2	1.1 ± 0.2	0.06	
LVAD surgery combined with				
Mitral valve repair	1 (13)	7 (28)	0.65	9 (23)
AV repair/closure	0 (0)	7 (28)	0.16	8 (21)
Tricuspid valve repair	1 (13)	2 (8)	1.0	4 (10)
PFO closure	1 (13)	—	0.24	1 (3)
Ramp test results				
LVEDD slope	−0.08 ± 0.04	−0.29 ± 0.11	<0.001	N/A
PI slope	−0.16 ± 0.04	−0.46 ± 0.20	<0.001	N/A
Power slope	0.74 ± 0.15	0.62 ± 0.17	0.03	N/A
Speed for complete AV closure	11,100 ± 1,146	9,124 ± 1,222	<0.001	
LDH value	1,737 ± 684	454 ± 263	<0.001	N/A
Low haptoglobin	<7	N/A	N/A	N/A
High plasma-free hemoglobin	19.1 ± 14.0	N/A	N/A	N/A
Length of follow-up, post-ramp test, days	171 ± 111	148 ± 89	0.6	N/A

Values are mean ± SD, n (%), or mean. *Two patients, 1 with a gross bend relief disconnect and 1 who is stable and being followed on a maximally intensified anticoagulation regimen are included in the all patient cohorts, but they were excluded in the confirmed device thrombosis versus no thrombosis patient chart.

AA = African American; IVS = interventricular septum; LDH = lactate dehydrogenase; LVAD = left ventricular assist device; N/A = not available; PFO = patent foramen ovale; other abbreviations as in Table 1.

non-normal distributions. Normality was assessed using the Shapiro-Wilk normality test. Receiver-operating characteristic curve analysis was done using the pROC package (11).

Table 3 Summary of Speed Optimization Ramp Tests (28 Tests)

Parameter	Set Clinical Speed Pre-Ramp Test	New Speed Post-Ramp Test
Average set speed, rpm	8,850 ± 431	8,850 ± 470
Change in speed pre- to post-test, rpm	N/A	Absolute speed change: 424 ± 211 Speed change in 17/28 tests: 61% Increased speed: 8 tests Mean increase speed change: 450 ± 177 Decreased speed: 9 tests Mean decrease speed change: −400 ± 245 No speed change: 11 tests
LVEDD, cm, mean ± SD	5.7 ± 1.2	5.7 ± 1.2
Blood pressure (MAP), mm Hg, mean ± SD	85.3 ± 9.7	86.1 ± 11.3
Frequency of aortic valve opening	Closed: 13 Open intermittently: 3 Open every beat: 6 Excluded for AV repair/closure at HMII implant: 6	Closed: 9 Open intermittently: 10 Open every beat: 3 Excluded for AV repair/closure at HMII implant: 6

HMII = HeartMate II; MAP = mean arterial pressure; other abbreviations as in Tables 1 and 2.

Each patient's LVEDD, PI, and power were plotted against device speed, ranging in value from 8,000 to 12,000 RPM in 400-rpm increments. The slopes for the lines were generated by fitting a linear function to each of the respective parameters using Excel 2007 software. The fit of the linear model was assessed using a correlation between LVEDD, PI, and power slopes and ramp speed.

Results

During the study period, 39 HeartMate II patients had a total of 52 ramp tests.

Demographics for the 39 patients are shown in Table 2. The mean age was 57 ± 14 years, 85% were men, 51% had dilated cardiomyopathy, 36% had diabetes mellitus, and 33% had a history of hypertension. Nine patients (23%) had undergone mitral valve repair, 8 (21%) AV repair, 1 (3%) AV closure, 4 (10%) tricuspid valve repair, and 1 (3%) patent foramen ovale closure at the time of HeartMate II surgical implantation.

Speed optimization. Twenty-eight ramp tests were performed for speed optimization. Device speed was changed in 17 (61%) of these tests, with a mean absolute value speed adjustment of 424 ± 211 rpm to achieve optimal LVEDD, AV opening, and MR as described previously.

Eight tests resulted in increased speeds for patients to allow for improved decompression of the LVEDD and a

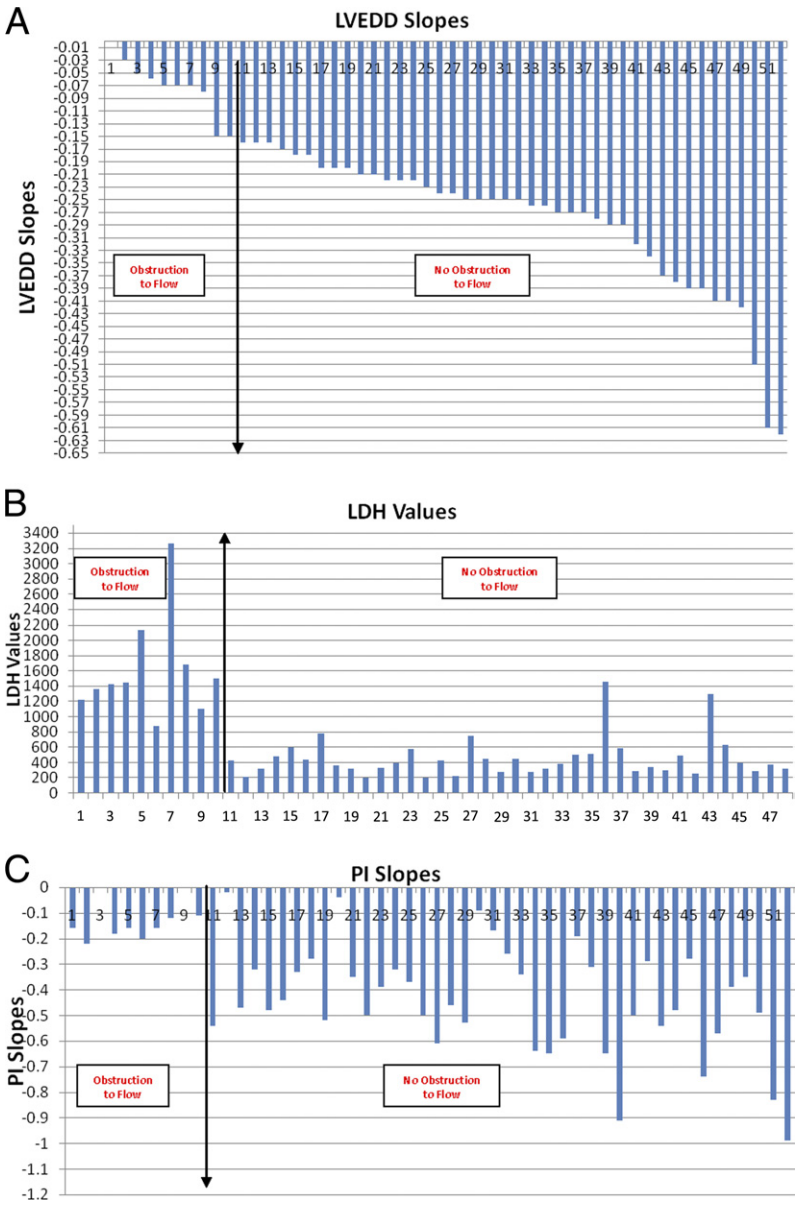

Figure 4 **Histograms of LVEDD, LDH, AV Closure Speeds, PI, and Power Slopes**

(A) LVEDD histogram; **(B)** LDH histogram; **(C)** PI histogram; **(D)** speed AV closer; **(E)** power. LDH = lactate dehydrogenase; other abbreviations as in Figure 3.

Continued on next page.

better interventricular septum position; the mean increased speed change was 450 ± 177 rpm. Nine tests resulted in decreased speeds for patients to allow for at least intermittent opening of the AV and to prevent leftward interventricular septum deviation; the mean decreased speed change was −400 ± 245 rpm. In 11 tests, the speed was not changed, and the programmed clinical speed was therefore validated as the optimal speed. The speed optimization results are summarized in Table 3.

The AVs in 6 of the 28 patients who underwent speed optimization tests were repaired and/or closed at the time of HeartMate II surgical implantation, and these patients were excluded from the AV optimization analysis. In the remaining 22 patients, AV opening occurred in 9 patients (41%) before and 13 patients (59%) after speed optimization. The AV of the remaining 9 patients did not open at the lowest pump speed that maintained adequate blood pressure with no more than mild MR.

Suspected device thrombosis. Ramp tests were performed in 17 patients for suspected device thrombosis. In 10 patients, the LVEDD changed only minimally with increasing speeds (Fig. 3B), whereas it changed more substan-

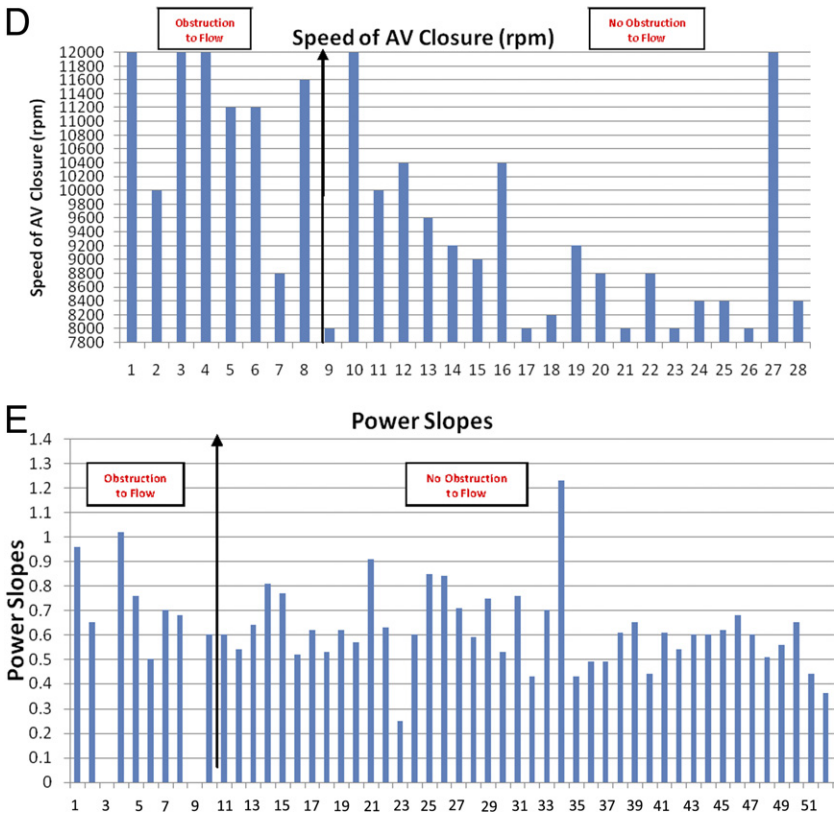

Figure 4 Continued

tially in the remaining 7 patients (Fig. 3A). Because of heightened concern over device thrombosis based on this finding, these 10 patients had their anticoagulation regimen maximally intensified and were observed for worsening hemolysis and/or evidence of end-organ dysfunction. The latter occurred in 9 of the 10 patients, and they underwent device exchange (n = 7), device explantation (n = 1), or urgent transplantation (n = 1). For these 9 patients, the mean time to surgery after the ramp test was 9.0 ± 9.0 days. One of the 10 patients remains stable on intensified anticoagulation.

Devices in all 9 patients were examined after explantation, and thrombus was found in 8. One patient did not have a thrombus, but instead had a grossly disconnected bend relief, which was functioning as a major obstruction to flow at the time of explantation. All patients who underwent device exchange or heart transplantation are alive without having experienced permanent end-organ damage. For the 8 patients with confirmed device thrombosis, the mean age was 53 ± 20 years, 62% were males, 50% had dilated cardiomyopathy, and 25% were African American (Table 2). The 7 patients whose ramp test demonstrated significant changes in LVEDD with increasing pump speed were monitored while on their original anticoagulation regimens. End-organ dysfunction developed in none of them, and none experienced thromboembolic events.

Ramp study results. LVEDD SLOPE. The LVEDD slope reflects a reduction in left ventricular size throughout the ramp study; thus, LVEDD slope is usually negative and the larger the absolute value of the slope is, the steeper the slope. The mean LVEDD slope was −0.08 ± 0.04 in confirmed device thrombosis patients, and −0.29 ± 0.11 in the remaining patients ($p < 0.001$). A histogram of the LVEDD slopes is shown in Figure 4A. All patients with confirmed device thrombosis or disconnected outflow bend relief and none of the remaining patients had an LVEDD slope >-0.16. Thus, an LVEDD slope of ≥-0.16 was diagnostic of flow obstruction, usually due to device thrombosis, but in 1 case, due to outflow bend relief disconnect.

PI SLOPE. The mean PI slope was −0.16 ± 0.04 in confirmed device thrombosis patients, and −0.46 ± 0.20 in the remaining patients ($p < 0.001$). All patients (100%) with confirmed device thrombosis and a recorded PI had a PI slope in the lower quartile (>-0.28), whereas only 5 patients (17.2%) with normal device function had a PI slope in the lower quartile. A histogram of the PI slopes is shown in Figure 4C.

Speed for complete closure of the AV. The mean speed at which the AV closed was 9,124 ± 1,222 rpm in the patients without confirmed thrombosis and 11,100 ± 1,146 rpm in those with confirmed thrombosis. The histograms of AV closure speed (Fig. 4D) show that the AVs of confirmed clot

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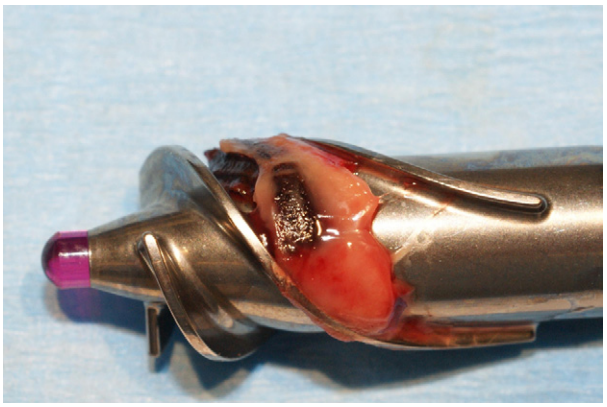


Figure 5 Confirmed Device Thrombosis on Explanted Device

patients closed at a much higher speed on average than the rest of the patient cohort without a clot.

Power slope. The mean power slope was 0.74 ± 0.15 in confirmed device thrombosis patients, and 0.62 ± 0.17 in the remaining patients ($p = 0.03$). A histogram of the power slopes is shown in Figure 4E.

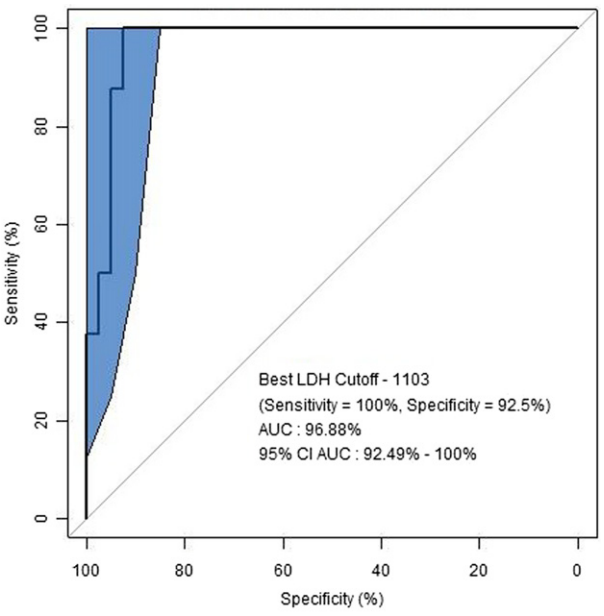
Of 52 tests, the speed was increased to 12,000 rpm in 15 tests without meeting the safety endpoints outlined previously. The ramp test was terminated before reaching 12,000 rpm in 37 patients; the mean speed at termination of the test in these patients was 10,573 ± 620 rpm. There was a total of 22 suction events during the ramp tests. The mean speed at which there was a suction event was 10,991 ± 856 rpm. There were no adverse events associated with any ramp tests. None of the tests resulted in sustained ventricular tachyarrhythmias. No suction events occurred in the cohort of patients with confirmed device thrombosis.

Ramp test results for 1 normal patient and 1 patient with device thrombosis are presented in Figures 3A and 3B, respectively. A flat LVEDD slope, an only slightly negative PI slope, and a dramatically high-power slope characterize a ramp test suggestive of device thrombosis. A device thrombosis visualized in the device impeller on explantation of the device is shown in Figure 5.

Lactate dehydrogenase. LDH levels were elevated in all patients with confirmed device thrombosis with a mean LDH level of 1,737 ± 684 IU/l. In addition, all had a haptoglobin <7 and the mean plasma free hemoglobin was elevated at 19.1 ± 14.0 mg/dl. Two patients had an elevated LDH level and signs of hemolysis but with the LVEDD slope <−0.16 threshold. These 2 patients were subsequently followed for 287 and 105 days, respectively, without signs of left-sided heart failure or any systemic embolization, and their devices were found to be without thrombus when explanted. A histogram of the LDH values is shown in Figure 4B. LDH levels were much higher in thrombosis patients compared with the remainder of patients with a mean LDH level of 454 ± 263 IU/l. Receiver-operating characteristic curve analysis for LDH as an indicator of thrombosis found that an LDH level >1,103 IU/l (5 times the upper limit of normal) has a sensitivity of 100% and a specificity of 92.5% (Fig. 6).

Discussion

In this study, we devised a unique, standardized clinical ramp test protocol to be routinely performed at the time of hospital discharge for speed optimization or if device malfunction is suspected. We developed a standardized methodology to analyze the ramp test results using the slopes (change in x/y on a graph) of the LVEDD, PI, and power combined with clinical parameters, such as LDH level. Our principal findings are as follows. First, the performance of a standardized ramp test was both safe and feasible in patients with CF-LVADs. Second, speed changes were made in 61% of patients when the test was performed for speed optimization. Third, the test proved to be highly sensitive and specific in the detection of obstruction to flow, namely, device thrombosis when used in conjunction with LDH level.



Threshold	Specificity	Sensitivity
750	85	100
786	87.5	100
1091	90	100
1300	92.5	87.5

Figure 6 ROC Curve Analysis of LDH as an Indicator of Device Thrombosis

The specificity and sensitivity values for LDH as an indicator for thrombosis were identified from the ROC curve. An LDH value >750 IU/l has a specificity of 85% and should trigger further evaluation for device thrombosis diagnosis. The optimal results were achieved with an LDH cutoff of 1,103 IU/l. The **blue region** of the graph represents a 95% confidence interval (CI) for the ROC curve using the bootstrap method in the pROC package (11) in R version 2.15.0. AUC = area under the curve; LDH = lactate dehydrogenase; ROC = receiver-operating characteristic.

Echocardiography has rapidly assumed a central role in understanding the complex patient–device interface. Topilsky et al. (6) reviewed the use of echocardiography for speed adjustment and elegantly characterized the relationship between LVEDD, optimal septum position, and severity of MR for optimal device support benefit. However, in their study, repeated echocardiographic imaging needed to be performed to achieve the stated goals. Slaughter et al. (12) recommended the performance of ramp tests on every patient after device implantation; these authors advised that tests be done in the operating room at the end of device implantation surgery with transthoracic echocardiography and hemodynamic monitoring. There is no doubt that this initial ramp test is important in the early postoperative care of patients with LVADs; however, immediate postoperative conditions will almost certainly be different from the conditions in which stable LVAD patients are discharged from the hospital. It is reasonable to assume that after optimization of volume status and weaning off both inotropic and vasoactive medications (12) before discharge, the relationship between device speed and optimal hemodynamics will be different from what it had been in the immediate postoperative period. Furthermore, the immediate postoperative goals for the device–patient interface may be different from those of long-term care. For example, in the initial phase, speed adjustment to allow for AV opening is not crucial to patient care. However, during the long-term phase of device treatment, there is a clear association of the AV remaining closed and the development of AI in patients supported by continuous-flow pumps (7).

Although advocated in the care of CF-LVAD patients, currently, no standardized clinical protocol for performance of a ramp test exists. Consequently, each medical center uses its own discretion for performing speed adjustments and diagnosing device malfunctions. Here we present the Columbia Ramp Study, which enumerates a standardized echocardiographically guided assessment of the relationship between the device and the patient, including study indications, contraindications, speed change intervals, echocardiographic parameters to measure, and a novel methodology for analyzing the data obtained with mathematical inference.

With a single study, the clinician gains an accurate understanding of the optimal device settings to preserve left ventricular geometry, reduce MR severity, and allow the AV to open intermittently. Routine application of this test allows for an overall characterization of the interface between the patient's native heart and the device. Importantly, each patient's baseline ramp test results also serve as an important reference with which to compare future test results, which may be done in the setting of suspected device thrombosis or device malfunction, much like a B-type natriuretic peptide level drawn during euvolemia.

Perhaps even more important than its use for speed optimization is the test's ability to aid in the diagnosis of pump thrombosis. Previous literature on CF-LVADs reported that the frequency of device thrombosis is in the range of 2% in the bridge-to-transplantation population (2) and 4% in the destination therapy population (1). Of note, a strict definition for device thrombosis was applied in the clinical trials:

> "Any obstructive thrombus in the device or its conduits associated with clinical symptoms of impaired pump performance (decreased pump flow, need to increase pump speed, increased power, hemolysis) or the need for thrombolytic or surgical intervention. In addition, pumps will be analyzed at Thoratec. Any severe thrombus scored as a level 3 thrombus (>50% obstruction) will be captured as an event" (1).

The true incidence of clinically relevant device thrombosis may be higher. The problem of device thrombosis will surely remain an important one as newer continuous-flow ventricular assist devices such as the HeartWare device (HeartWare International) are introduced into clinical practice.

Risk factors for device thrombosis have been reported and include less aggressive anticoagulation, infection, and hypercoagulability syndromes (i.e., systemic lupus erythematosus). One barrier in the treatment of patients with device thrombosis stems from the difficulty in making this diagnosis before catastrophic thromboembolic events. Currently, suspicion of thrombosis arises when there are signs of hemolysis (elevated LDH, high plasma free hemoglobin, and low haptoglobin levels), transient increases in device power >14 days post-implantation, or recurrence of congestive heart failure (1). However, these criteria lack both sensitivity and specificity for the diagnosis of device thrombosis. Regular echocardiography typically fails to diagnose the majority of device thromboses (13,14). CT scan with contrast media has been proposed as a diagnostic option for inflow and outflow cannulas thrombosis (15,16), but is a severely limited approach because thrombus within the device cannot be detected.

In the current study, we observed that the ramp test can identify a perturbation of the relationship between the patient's native heart and the device. We demonstrated that LVEDD slope correlates with device thrombosis and/or severe outflow obstruction due to a disconnected bend relief. This finding is explained by the fact that the impediment to flow caused by device thrombosis leads to an uncoupling of the relationship between the device speed and LVEDD. In other words, blunted reductions in LVEDD in response to an increase in pump speed indicate an obstruction to flow through the device. Not surprisingly, LVEDD slopes were the most accurate measure in the diagnosis of thrombosis. The combination of clinical suspicion for thrombosis based on heart failure symptoms, LDH levels, LVEDD, PI, and power slopes led us to intensify anticoagulation regimens and/or perform device exchange in 8 patients, 7 (88%) of whom were found to have device thrombosis, with the eighth patient having an obstruction to flow due to a gross bend relief disconnect.

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Study limitations. First, this was a single-center, prospective analysis of a relatively small cohort of patients. Second, our method for definitive diagnosis of pump thrombosis was to send suspected thrombosis pumps to Thoratec Corporation after explantation at Columbia University Medical Center for further inspection of the pump housing and final validation of device clot. This may introduce selection bias. Our current practice is to send all explanted pumps, including both "normal" and malfunctioning pumps to the manufacturer for disassembly and inspection. Third, the ramp test protocol is time-consuming and cumbersome in that it requires strict adherence to the 2-min time interval between speed designations. This ramp test protocol may be able to be abbreviated once a larger dataset is reviewed. We designed a protocol to be used with the HeartWare device, and preliminary results are indicative of the ramp test being a beneficial tool for speed adjustment and device malfunction diagnosis.

Further follow-up is needed on the patients who underwent the ramp test for speed optimization for outcome evaluation, the development of AI, and frequency of device-related complications.

Recommendation. Based on our experience at Columbia University Medical Center, we developed a working algorithm to facilitate the diagnosis of device malfunction (Fig. 7).

Conclusions

Ramp tests performed to monitor appropriateness of CF-LVAD programmed settings very frequently led to changes in device speed and, therefore, should be done routinely in CF-LVAD recipients. Ramp tests allowed device malfunction detection in the setting of suspected device thrombosis, and, pending validation in larger studies, they may be used to monitor the effects of therapeutic interventions and to determine the need for surgical intervention.

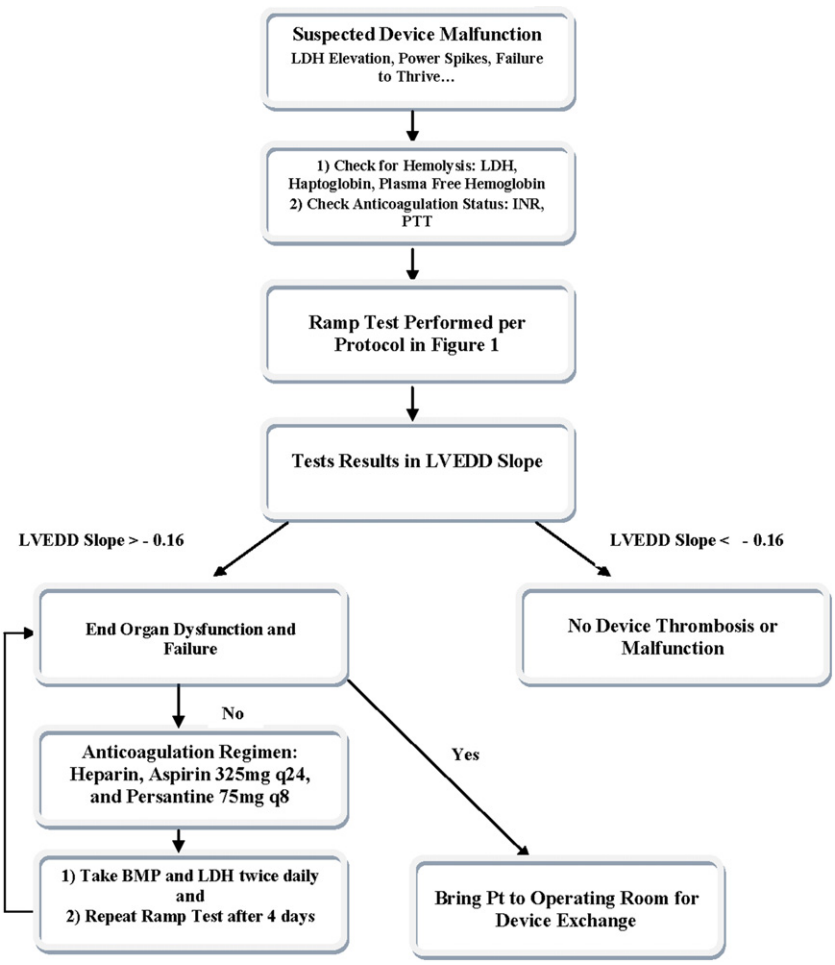

Figure 7 Suspected Device Malfunction Algorithm

Suggested management algorithm for patients with suspected device thrombosis. BMP = basic metabolic panel; Pt = patient; other abbreviations as in Figures 1 and 3.

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Key Words: device thrombosis ■ LVAD ■ LVEDD ■ ramp test.

APPENDIX

For supplemental tables, please see the online version of this article.