

EDITORIAL COMMENT

Left Ventricular Assist Devices Ramp Studies



Truth or Consequences?*

Randall C. Starling, MD, MPH

In this issue of *JACC: Heart Failure*, Adaya et al. (1) from the University of Minnesota prospectively investigated patients who received the Thoratec HeartMate II (Pleasanton, California) left ventricular assist device (LVAD) between June 2012 and February 2014. The investigators designed a prospective investigation to evaluate the incremental data provided by echocardiographic ramp studies. In 2012, Uriel et al. (2) described a novel technique (ramp study) that used echocardiographic techniques to assess the impact of changes in LVAD speed (rotations per minute) and the relation to LVAD power, the

SEE PAGE 291

pulsatility index, LVAD flow, and left ventricular end-diastolic diameter (LVEDD). Uriel et al. (2) reported their prospective study at Columbia University Medical Center in 39 patients who underwent 52 ramp studies. The Columbia group suggested that ramp studies should be performed routinely to optimize LVAD speed to provide optimal unloading; they also noted that the ramp study slope (LVEDD/incremental speed changes in LVAD) could predict LVAD malfunction and need for surgical intervention, including urgent transplantation or LVAD exchange (2). The Columbia ramp study required full anticoagulation, reducing the LVAD speed to 8,000 rpm,

echocardiographic measures at baseline, and sequential measures every 2 min as the pump speed was increased by increments of 400 rpm up to a speed of 12,000 rpm. Seventeen patients underwent ramp studies for suspected pump thrombosis and 10 had minimal change in LVEDD with the ramp study. The Columbia investigators confirmed pump thrombosis in 8 of 9 cases at the time of emergent device exchange, removal, or urgent transplantation. One patient remained stable on intensified anticoagulation. All 10 patients with suspected pump thrombosis but none of the remaining 7 had an LVEDD slope > -0.16 .

The current investigation was designed to determine the limitations of the ramp study and to specifically determine how loading conditions might affect the results. Because the ramp study was on the basis of the slope of change in LVEDD, which is a measure of left ventricular unloading, the investigators hypothesized that both aortic insufficiency (AI) and elevated mean arterial pressure (MAP) might result in an abnormal LVEDD slope and a false positive study indicative of device malfunction related to pump thrombosis. In addition, the investigators hypothesized that pump thrombus that was “nonobstructive” to flow could be present, and that the LVEDD slope would remain normal with increases in pump speed.

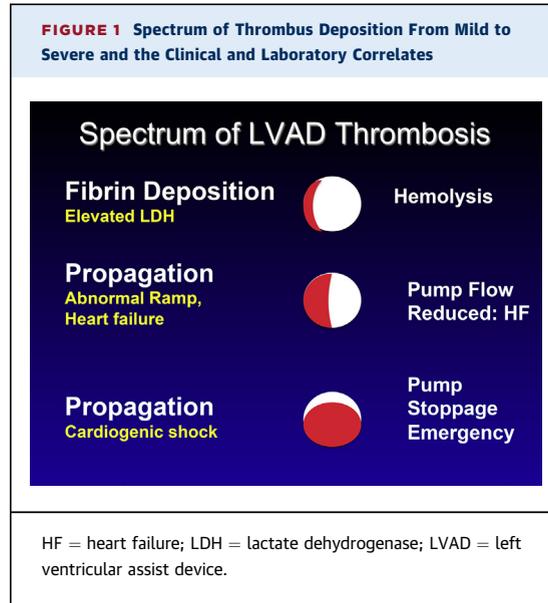
During the study, the investigators collected comprehensive clinical, laboratory, device and echocardiographic data at each visit. Seventy-eight ramp studies were performed in 55 patients. There were 36 abnormal ramp studies based upon slope. Eighteen of the ramp studies were true positives for pump thrombosis, and 18 were false positives. The 18 false positives included 10 studies in 7 patients with significant AI and 6 studies in 6 patients with $MAP \geq 85$ mm Hg. There was no significant difference

*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

From the Kaufman Center for Heart Failure, Heart and Vascular Institute, Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio. Dr. Starling serves on the Thoratec-sponsored ROADMAP clinical trial steering committee (this is an unpaid position; he serves as an unpaid advisor to HeartWare Inc.; and is a co-principal investigator for the MVAD trial.

in mean LVEDD slope between the false positive tests; however, the mean lactate dehydrogenase (LDH) was significantly lower in the false positive ramp group (954 vs. 3,379 U/l; $p < 0.001$). Of the 13 ramp tests in patients with AI, 10 tests (77%) showed an abnormal LVEDD slope (≥ -0.16), but none of these patients had clinical suspicion of LVAD obstruction or hemolysis. The ramp studies in the true positive patients and the patients with significant AI did not differ by LVEDD slope; however, the LDH levels were significantly lower in the AI group versus the true positive group (1,301 vs. 3,379; $p = 0.001$). In patients with MAP ≥ 85 mm Hg, a trend was seen for a steeper slope in patients without device thrombosis, but the difference was not significant. Ramp test parameters were similar in those with MAP ≥ 85 mm Hg and true positive results; however, again, the LDH levels differed and were lower in those with MAP ≥ 85 mm Hg versus those who had true positive results (1,188 vs. 3,379; $p = 0.001$). The investigators clearly demonstrated that LVEDD slope is abnormal in patients with significant AI or MAP ≥ 85 mm Hg in the absence of pump thrombosis; however, the lack of LDH elevation allowed the exclusion of significant pump thrombus deposition. This is a very important observation in the context of management and morbidity of LVAD pump thrombosis. An incorrect diagnosis could result in exposure to treatment associated with significant risk. The Minnesota series described 13 patients with confirmed pump thrombosis; 2 died, 2 underwent urgent transplantation, and 9 (69%) had LVAD exchange. The Interagency Registry for Mechanically Assisted Circulatory Support registry showed that mortality with device exchange is greater than a primary LVAD implant (3). Medical management of device thrombosis is not evidence based and is associated with significant morbidity and mortality in conjunction with the use of thrombolytic therapies (4). Uriel et al. (2) proposed using the LVEDD slope to definitively diagnose pump thrombosis. Adatya et al. (1) demonstrated that the area under the curve (AUC) for LVEDD slope alone in their series was 0.76 using the slope cutoff of -0.16 proposed by Uriel et al., which increased to 0.88 when removing patients with significant AI from the study. Importantly, the investigators found that the AUC for the combination of LVEDD slope and LDH concentration was 0.96.

The current approach to the diagnosis and treatment of LVAD thrombosis is on the basis of the level of evidence C (5). The findings of this study provided important incremental guidance to identify patients with pump thrombosis.



Why does LVEDD slope remain normal in some patients with abnormal LDH? The LVAD rotar may have minimal deposition of thrombus and hemolysis without hemodynamic consequences (Figure 1). LDH appears to be an early marker of pump thrombus deposition, and abnormal LVEDD slope likely occurs later as the amount of pump thrombus increases. The time course of these events is probably highly variable and may be related to many clinical and device specific factors. The results of this investigation are quite timely and clinically important, as Jorde et al. (6) recently reported in a large series of HeartMate II LVAD patients in which 37.6% of patients developed moderate or greater AI after 3 years of support. AI is an important and common complication in recipients of continuous flow LVAD that is believed to be related to the degree of LV unloading and aortic valve opening (7). Finally, the occurrence of pump thrombosis appears to be increasing compared with the original reports in the pivotal clinical trials. Therefore, the need for early detection of pump thrombosis, which is associated with high morbidity and mortality, is of paramount importance (3,8). Adatya et al. (1) provide important new insights with regard to the limitations of the LVEDD slope to identify the presence of pump thrombosis and the importance of loading conditions in ramp studies. Furthermore, the investigators reinforce the importance of using echocardiographic data and serial measures of LDH to identify pump thrombosis, and they demonstrate the poor outcomes in patients with this complication of LVAD therapy.

REPRINTS AND CORRESPONDENCE: Dr. Randall C. Starling, Desk J3-4, Kaufman Center for Heart Failure, Heart and Vascular Institute, Department of

Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Avenue, Cleveland Ohio 44195. E-mail: starlir@ccf.org.

REFERENCES

1. Adatya S, Holley CT, Roy SS, et al. Echocardiographic ramp test for continuous-flow left ventricular assist devices: do loading conditions matter? *J Am Coll Cardiol HF* 2015;3:291-9.
2. Uriel N, Morrison KA, Garan AR, et al. 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. *J Am Coll Cardiol* 2012;60:1764-75.
3. Kirklin JK, Naftel DC, Kormos RL, et al. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) analysis of pump thrombosis in the HeartMate II left ventricular assist device. *J Heart Lung Transplant* 2014;33:12-22.
4. Schlendorf K, Patel CB, Gehrig T, et al. Thrombolytic therapy for thrombosis of continuous flow ventricular assist devices. *J Card Fail* 2014;20:91-7.
5. Goldstein DJ, John R, Salerno C, et al. Algorithm for the diagnosis and management of suspected pump thrombus. *J Heart Lung Transplant* 2013;32:667-70.
6. Jorde UP, Uriel N, Nahumi N, et al. Prevalence, significance, and management of aortic insufficiency in continuous flow left ventricular assist device recipients. *Circ Heart Fail* 2014;7:310-9.
7. Cowger J, Pagani FD, Haft JW, Romano MA, Aaronson KD, Kolas TJ. The development of aortic insufficiency in left ventricular assist device-supported patients. *Circ Heart Fail* 2010;3:668-74.
8. Starling RC, Moazami N, Silvestry SC, et al. Unexpected abrupt increase in left ventricular assist device thrombosis. *N Engl J Med* 2014;370:33-40.

KEY WORDS echocardiography, left ventricular assist device, LVAD, pump thrombosis, ramp study, thrombosis