Repeated Ramp Tests on Stable LVAD Patients Reveal Patient-Specific Hemodynamic Fingerprint

Teruhiko Imamura,* Daniel Burkhoff,† Daniel Rodgers,* Sirtaz Adatya,* Nitasha Sarswat,* Gene Kim,* Jayant Raikhelkar,* Takeyoshi Ota,‡ Tae Song,‡ Colleen Juricek,‡ Valluvan Jeevanandam,‡ Gabriel Sayer,* and Nir Uriel*

Hemodynamic speed ramp tests are used in left ventricular assist device (LVAD) patients to guide speed adjustment and medical therapies. However, the reproducibility of these tests is unknown. In this prospective study, clinically stable LVAD patients underwent echocardiography and right heart catheterization ramp tests followed by a repeat test within 2 years as per institutional protocol. Sixteen patients (61.8±10.5 years old, 50% male, eight with HeartMate II and eight with HVAD) underwent repeated ramp testing. The first test was performed 187 (42–1857) days from LVAD implant and the second test was performed 278 (126–560) days from the first test. All hemodynamic variables measured at the baseline speed remained statistically unchanged between the first and second ramp test ($p > 0.05$ for all). Changes in hemodynamic parameters, as assessed by the slopes of their changes over the range of speeds tested, were also the same at the two timepoints ($p > 0.05$ for all). Stable LVAD patients had similar hemodynamic profiles over the course of years including similar responses to speed changes. This suggests that ramp tests may represent a hemodynamic fingerprint; deviations from a baseline test can aid diagnosis at times of clinical deterioration or device malfunction. *ASAIO Journal* 2017; XX:00–00.

Key Words: heart failure, unloading, inotropes

Continuous flow left ventricular assist devices (LVADs) have dramatically improved the survival rate of patients with stage D heart failure (HF)[1–4] and have been increasingly used as both bridge to transplantation (BTT) and as destination therapy (DT).[5] Since the duration of support is increasing, especially in the context of DT, attention is shifting to ways to reduce adverse events and improve patients' quality of life.[6]

Multiple factors are believed to be contributing to device preference: 1) optimization of medical therapy and 2) optimization of LVAD device speed.[7] These are important determinants of the hemodynamic support delivered by the LVAD, such as total blood flow, arterial pressure, and ventricular filling pressures. Those hemodynamics parameters determinants exercise tolerance, New York Heart Association functional class, and overall quality of life.[8] However, existing guidelines are vague regarding how to optimize both the medical therapy and device speed during support.

The International Society for Heart and Lung Transplantation recommends the adjustment of rotation speed using echocardiography, targeting sufficient LV unloading while maintaining LV septum in the midline position, minimizing the degree of mitral valve regurgitation (class of recommendation: I; level of evidence: C), and allowing for intermittent aortic valve opening (class of recommendation: IIb; level of evidence: B).[9] However, these suggested indexes are not necessarily quantitative, and the practical adjustment of rotation speed may vary depending on the attending physicians. Medical management recommendation are equally vague, indicating that diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, and mineralocorticoids are considered useful for managing volume status, blood pressure, arrhythmias, and myocardial fibrosis (class of recommendation: I; level of evidence: C).

We recently described a hemodynamic and echocardiographic speed ramp test in a study of patients implanted with either HVAD or HeartMate II devices.[10] Despite pretest classification of all patients as being clinically stable and optimized, we observed extremely wide variability in all hemodynamic parameters, including pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and total blood flow. Accordingly, we proposed means of using these ramp tests to guide adjustments of medical therapy and LVAD speed based on patient-specific RPM-dependent changes in CVP, PCWP, and cardiac output.

However, the reproducibility and patient-specificity of these RPM-dependent hemodynamic patterns over time and sensitivity to changes in medical management and patient conditions are unknown. In the present study, patients underwent two clinically indicated hemodynamic LVAD speed ramp tests. Changes in medications and clinical conditions were noted between the two tests. We hypothesized that in a stable patient, this pattern would provide a hemodynamic "fingerprint," deviations from which could aid diagnosis at times of clinical deterioration or device malfunction.

From the *Department of Medicine, University of Chicago Medical Center, Chicago, Illinois; †Columbia University Medical Center, and Cardiovascular Research Foundation, New York, New York; and ‡Department of Surgery, University of Chicago Medical Center, Chicago, Illinois.

Submitted for consideration April 2017; accepted for publication in revised form September 2017.

Disclosure: The authors have no conflicts of interest to report.

Teruhiko Imamura receives financial funding from Japan Heart Foundation/Bayer Yakuhin Research Grant Abroad and Postdoctoral Fellowship for Research Abroad of Japan Society for the Promotion of Science. Nir Uriel receives consultant fee and grant support from Abbott and Medtronic. Valluvan Jeevanandam receives consultant fee from Abbott. Daniel Burkhoff is a consultant to HeartWare division of Medtronic and receives educational grant support from Abiomed.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML and PDF versions of this article on the journal's Web site (www.asaiojournal.com).

Correspondence: Nir Uriel, Department of Medicine, University of Chicago Medical Center, 5841 S. Maryland Avenue, Chicago, IL 60637. Email: nuriel@medicine.bsd.uchicago.edu.

DOI: 10.1097/MAT.0000000000000705

Methods

Patient Selection

In this prospective study, 16 consecutive patients receiving a LVAD implant (eight HeartMate II [St. Jude Medical, Inc., Pleasanton, CA] and eight HVAD [HeartWare International, Inc., Framingham, MA]) who underwent two clinically indicated speed ramp tests with hemodynamic monitoring within 2 years were included. All patients were clinically stable outpatients (*i.e.*, specifically not admitted for HF) during the study period; patients suspected of device thrombosis were not included. All participants received the second ramp tests to maintain optimal LVAD speed setting as a routine clinical practice. The University of Chicago's institutional review board committee approved this study and all patients signed informed consents before enrollment.

Speed Ramp Test

All patients received standard speed ramp tests with echocardiographic and hemodynamic monitoring as previously described.[10] In brief, patient's hemodynamics was measured with right heart catheterization; echocardiography was performed at every speed. Cardiac output and cardiac index were calculated by the indirect Fick method. HVAD patients' device speeds were lowered to 2,300 RPM and HeartMate II patients' device speeds were lowered to 8,000 RPM. After at least a 2 minute stabilization period, echocardiographic and hemodynamic parameters were measured. After completing these measurements, device speeds were increased by 100 RPM for HVAD patients and by 400 RPM for HeartMate II patients followed by repeat measurement of all parameters 2 minutes after speed change. This procedure was repeated until one of the following three were achieved: 1) reaching the maximum of 3,200 RPM for HVAD patients or 12,000 RPM for HeartMate II patients; 2) if any suction events occurred; or 3) if the left ventricular end-diastolic diameter decreased to less than 3.0 cm. At the conclusion of each test, the attending cardiologist set at the speed wherein hemodynamic normalization was achieved *i.e.*, PCWP <18 mm Hg and CVP <12 mm Hg with the secondary goals of minimizing mitral regurgitation and intermittent aortic valve opening.[9]

Data and Statistical Analyses

The primary analysis was based on comparisons of plots of CVP *versus* PCWP between the two time points. For these analyses, the normal range was set between 8 and 18 mm Hg for PCWP and between 5 and 12 mm Hg for CVP, as previously described.[10]

All statistical analyses were performed using SPSS Statistics 22 (SPSS Inc., Chicago, IL) and a p value less than 0.05 was considered as statistically significant. Data are expressed as mean ± standard deviation. Continuous variables were compared using the unpaired t test or Mann–Whitney U test as appropriate, and categorical variables were compared using the χ^2 test or Fisher's exact test as appropriate. Slopes of each variable as a function of RPM step were calculated using linear regression as previously described; these slope values indicate the degree of change with incremental changes of rotation speed.[11] Comparison of clinical data between the first and second ramp speed tests was performed using paired t test. In the CVP–PCWP curve, the centroid of each curve was calculated from an average of CVP and PCWP values. The slopes of line between the origin and the centroid were compared by paired t test between two tests.

Results

Baseline Characteristics

Sixteen patients were enrolled to our study, mean age was 61.8 ± 10.5 years old and 50% were males. All patients completed ramp tests without any complications. Patient baseline characteristics are summarized in **Table 1**. The majority of patients were implanted as DT (63%), and 38% had HF with nonischemic etiology. Eight patients received a HeartMate II and eight patients received an HVAD. The median interval between LVAD implantation and the first ramp test was 187 days (range 42–1857 days) and all patients were clinically stable outpatients without reports of HF symptoms before the first test. The second ramp test was performed at a median of 278 days (range 126–560 days) after the first test.

Clinical Course and Management Between Tests

Between the first and second test, no patient was admitted to the hospital for HF and none had any significant complaints related to HF when seen in the outpatient setting. There were a total of three hospitalizations in three patients, one for INR control, one for cardiac resynchronization therapy lead infection, and one for cerebrovascular accident (which ultimately resolved without significant residual deficit).

Between the first and second test, the dose of diuretic was decreased in 6 patients (by an average of 66.7 ± 53.2 mg/day, from 116.7 ± 80.4 to 50.0 ± 43.4 mg/day furosemide), unchanged in 7 patients, and increased in 3 patients (by an average of 40.0 ± 20.0 mg/day, from 20.0 ± 20.0 to 60.0 ± 34.6 mg/day). An overview of all medical changes is summarized in **Table 2**.

Table 1. Baseline Characteristics

	Total (N = 16)
Demographics	
Age (years)	61.8 ± 10.5
Gender (male)	8 (50%)
Race (Caucasian)	4 (25%)
Nonischemic etiology	6 (38%)
Body height (cm)	171.2 ± 11.3
Body weight (kg)	89.2 ± 19.6
HeartMate II	8 (50%)
HVAD	8 (50%)
Timing of speed ramp test	
Days from surgery to first test	187 (42–1857)
Days from first to second test	278 (126–560)
Comorbidity	
Destination therapy	10 (63%)
Diabetes mellitus	7 (44%)
Hypertension	8 (50%)
Peripheral artery disease	0 (0%)
Atrial fibrillation	6 (38%)
History of ventricular tachyarrhythmia	2 (13%)
Chronic obstructive lung disease	3 (19%)

Table 2. Patients Number of Each Medication Change

Dose	Diuretic	β-Blocker	ACEI or ARB	Aldosterone Antagonist
Increased	3	3	8	4
Unchanged	7	11	6	8
Decreased	6	2	2	4

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Comparison of Variables Between the First and Second Speed Ramp Test

Echocardiographic and hemodynamic variables at the baseline speed were statistically comparable between the first and second ramp tests (**Table 3**; $p > 0.05$ for all). Similarly, the RPM-dependent hemodynamic changes (reported as slopes of the relationship between the respective parameter and RMP step) did not differ between the two tests ($p > 0.05$ for all). The results were the same when HeartMate II and HVAD patients were analyzed separately (see Tables 1 and 2, Supplemental Digital Content, http://links.lww.com/ASAIO/A208). Similar results were also observed between DT group (N = 10) and bridge to transplant group (N = 6) and between ischemic etiology group (N = 10) and nonischemic etiology group (N = 6) (data not shown).

Comparison of Central Venous Pressure and Pulmonary Capillary Wedge Pressure Between First and Second Tests

Changes in CVP and PCWP stratified by changes in diuretic doses are summarized in **Figure 1A, B**, respectively. CVP decreased significantly with increasing diuretic doses (**Figure 1A**; $p < 0.05$). There was a trend for PCWP to decrease with increasing diuretic doses (**Figure 1B**; $p < 0.10$).

The relationship between CVP and PCWP in all patients at the baseline RPM and at the final RPM setting are shown in **Figure 2**. At the baseline speed of the first test, 3 patients (19%) were outside the normal range (**Figure 2A**); after adjustment of speed (from 9168.8±441.7 to 9321.3±522.5 RPM in HeartMate II and 2635.0±109.9 to 2712.5±157.8 RPM in HVAD), the points migrated downward and leftward and only two patient remained abnormal with elevated CVP and normal PCWP (*i.e.*, in the right HF zone, **Figure 2B**). At baseline speed on the second test (**Figure 2C**), the CVP–PCWP points migrated toward higher pressures and three patients were outside of the normal zone. After additional RPM adjustments based on the ramp test, two patients still remained outside the normal zone (**Figure 2D**). At the baseline speed, the relationships between CVP and PCWP, which was assessed by PCWP/CVP ratio, were comparable between the first and second tests (2.00±0.94 *vs.* 2.08±0.72; $p = 0.695$).

Changes in Central Venous Pressure–Pulmonary Capillary Wedge Pressure Relationship

Central venous pressure–pulmonary capillary wedge pressure relationships of individual patients during the two speed ramp tests are shown in **Figure 3** (for patients whose diuretic dose was the same between tests), **Figure 4** (for patients whose diuretic dose was decreased between tests), and **Figure 5** (for patients whose diuretic dose increased between tests). In each case, PCWP is plotted as a function of CVP at all LVAD speeds during the test.

In each case, the shape and general position of the CVP–PCWP relationship curve were unique and relatively preserved from the first to the second test independent of whether diuretics were changed or not.

Table 3. Comparison of Clinical Variables Between the First and Second Ramp Testing

	1st Ramp	2nd Ramp	*p* Value
Variables at baseline speed			
Rotational speed (HeartMate II) (rpm)	9168.8±441.7	9197.5±397.2	0.84
Rotational speed (HVAD) (rpm)	2635.0±109.9	2707.5±169.3	0.14
LVDd (cm)	5.93±1.13	5.73±1.06	0.33
PCWP (mm Hg)	12.2±5.6	13.6±6.1	0.40
CI (L/min/m^2)	2.87±0.49	2.66±0.46	0.080
PAM (mm Hg)	21.4±5.4	23.4±7.9	0.33
Heart rate (bpm)	84.6±10.1	80.3±7.2	0.14
RVSWI (g/m^2)	7.08±2.58	8.10±2.59	0.29
CVP (mm Hg)	6.7±3.9	7.4±4.3	0.43
PVR (WU)	1.68±0.69	1.94±1.07	0.28
PAPi	3.10±1.61	3.64±4.31	0.53
Slopes during ramp testing			
LVDd slope (cm/step)	–0.16±0.11	–0.13±0.12	0.17
PCWP slope (mm Hg/step)	–0.93±0.41	–0.68±0.80	0.31
CI slope (L/min/m^2/step)	0.056±0.089	0.051±0.026	0.84
PAM slope (mm Hg/step)	–0.75±0.48	–0.52±0.81	0.28
RVSWI slope (g/m^2/step)	–0.125±0.298	0.002±0.266	0.21
CVP slope (mm Hg/step)	–0.16±0.25	–0.10±0.25	0.39
Medications			
β-blocker	11 (69%)	12 (75%)	0.69
ACEI or ARB	10 (63%)	13 (81%)	0.24
Aldosterone antagonist	8 (50%)	7 (44%)	0.50
Diuretics	14 (88%)	14 (88%)	1.00

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, cardiac index; CVP, central venous pressure; LVDd, left ventricular diastolic diameter; PAM, mean pulmonary artery pressure; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RVSWI, right ventricular stroke work index.

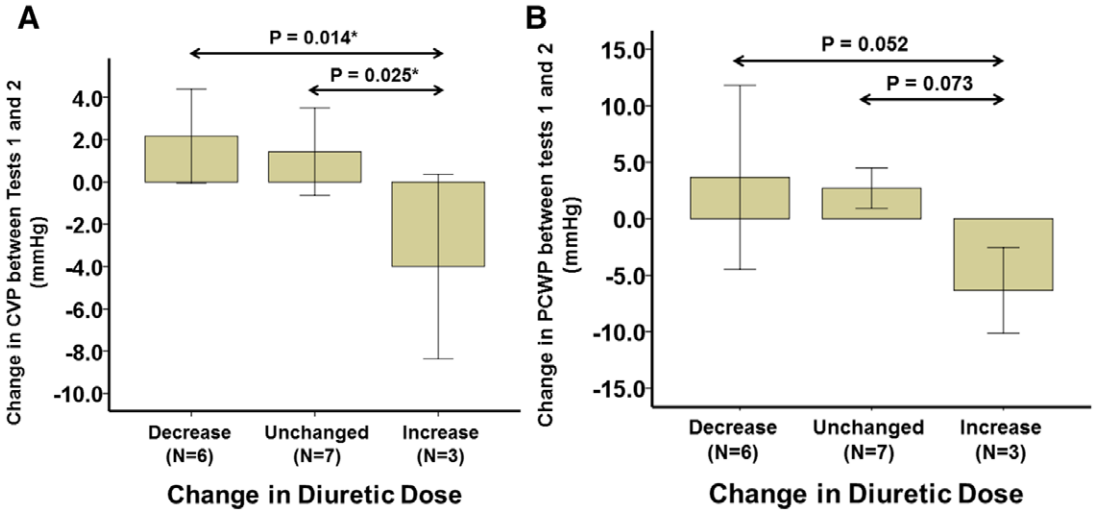

Figure 1. Changes in CVP (A) and PCWP (B) between two tests stratified by the changes in dose of diuretic between two tests, *i.e.*, decrease, unchanged, and increase group. CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure.

Consistently, the slopes of centroid in each curve were preserved between two tests (2.10 ± 1.43 *vs.* 1.93 ± 0.65; $p = 0.56$). An example of comparison of centroid slopes between two tests is shown in Figure 1 (Supplemental Digital Content, http://links.lww.com/ASAIO/A209).

Discussion

In this prospective study, we performed two standard hemodynamic speed ramp tests within 2 years in clinically stable LVAD outpatients and found that the CVP–PCWP relationship is reasonably reproducible, falling on nearly the same line, and

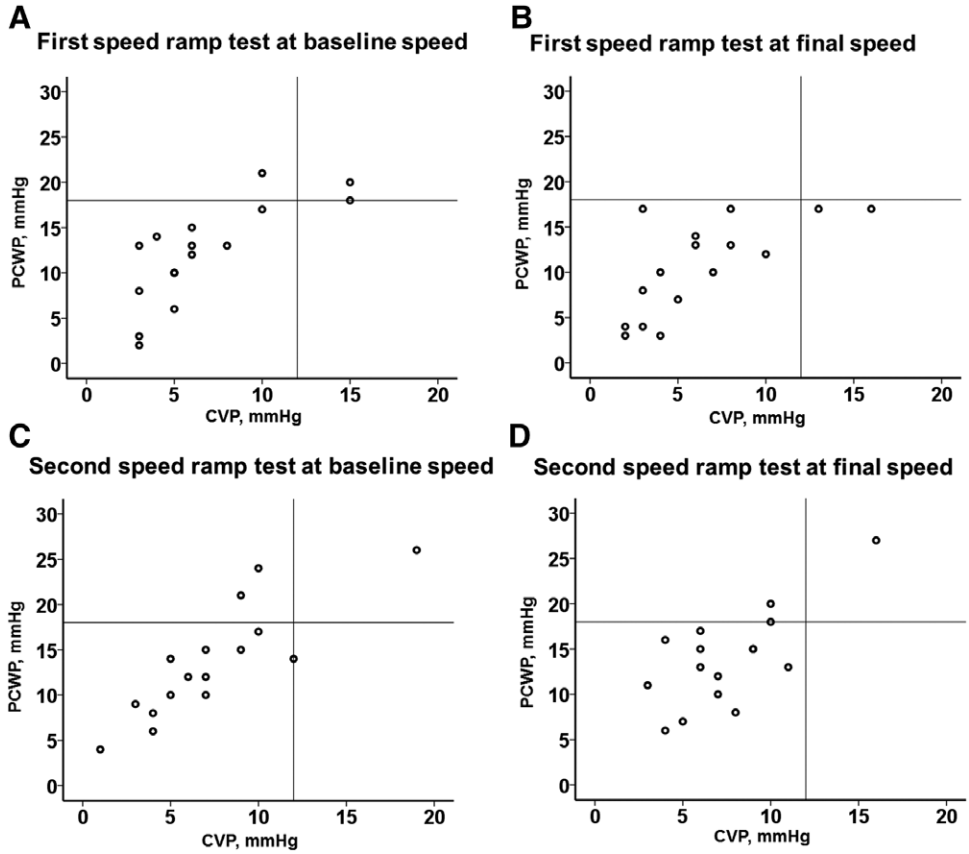

Figure 2. Plots of individual patients' CVP and PCWP. Plots are divided into four zones by CVP 12 mm Hg and PCWP 18 mm Hg: normal (lower left), left heart failure (upper left), fluid overload (upper right), and right heart failure (lower right). First test results at baseline speed setting (A) and final speed setting (B). Second test results at baseline speed setting (C) and final speed setting (D). CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure.

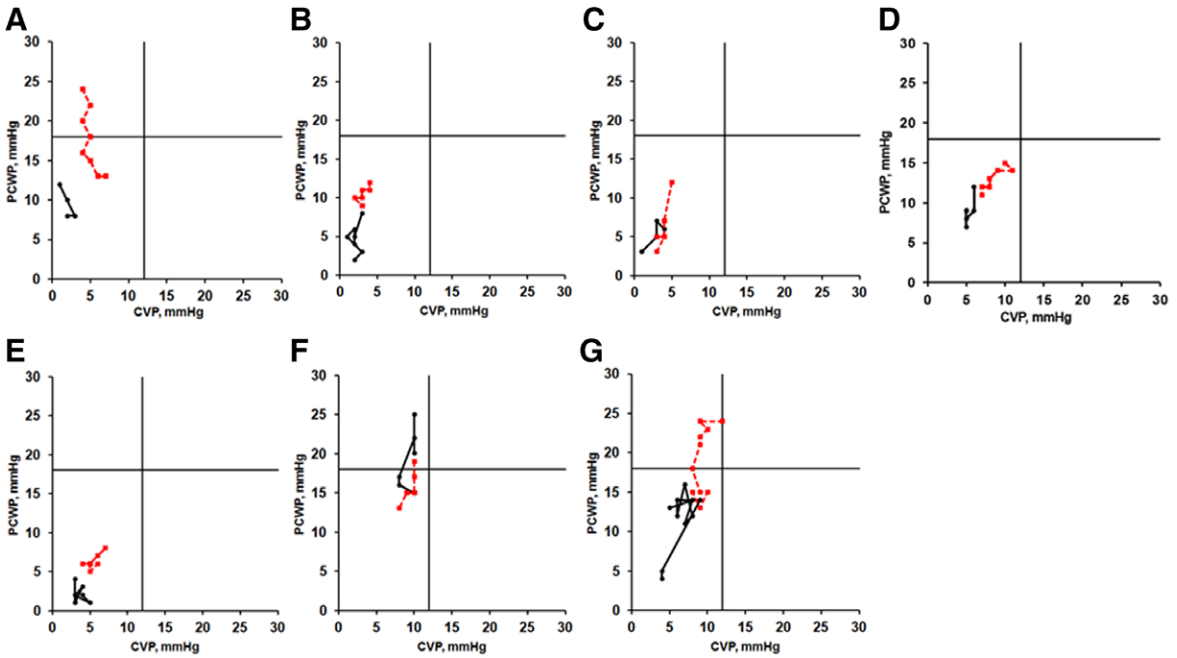

Figure 3. CVP–PCWP relationships of individual patients during the two speed ramp tests for those whose diuretic dose remained unchanged. Black bar represents the first test and red bar represents the second test. CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure.

that its characteristics are relatively unique to a given patient. This is despite that fact that, as observed previously,[10] there is a very wide variability in absolute values of these hemodynamic parameters between patients. In response to medication changes, there were minor shifts of the CVP–PCWP relationship. In all cases, however, the shape of the curve was reasonably well preserved. Accordingly, in hemodynamically and clinically stable LVAD patients, this relationship appears to

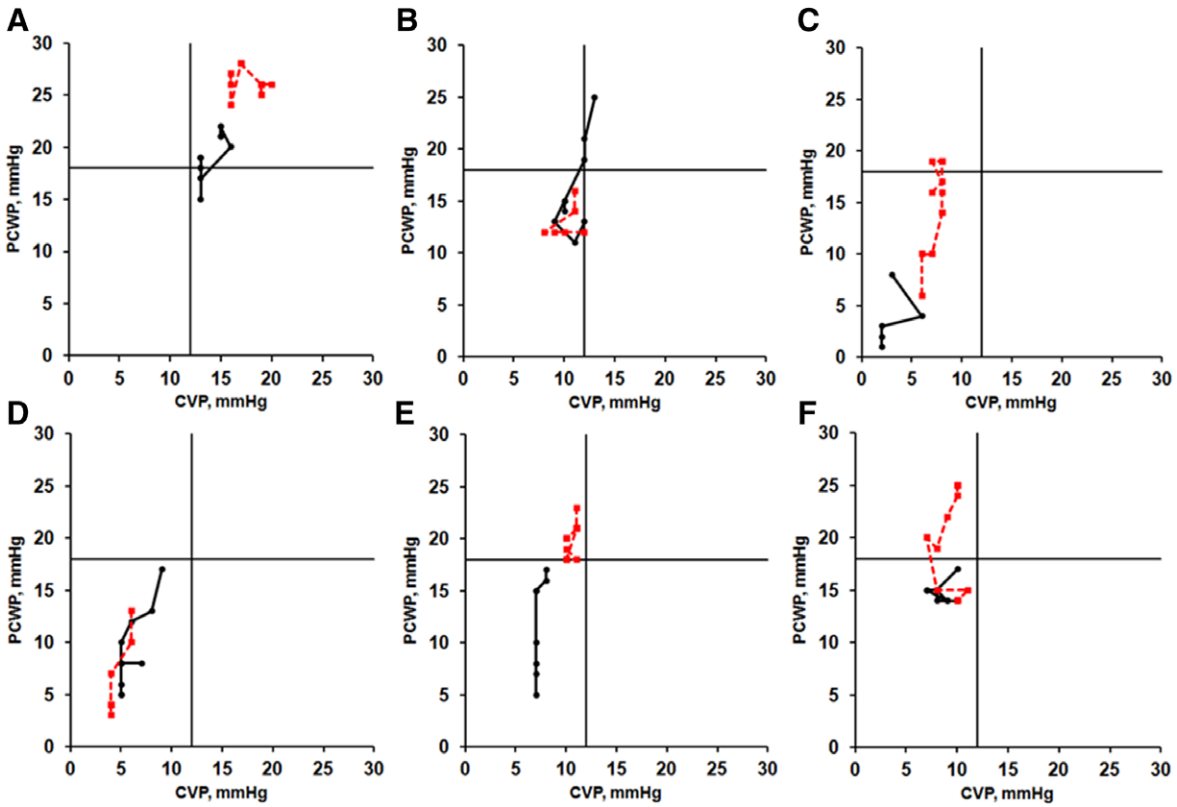

Figure 4. CVP–PCWP relationships of individual patients during the two speed ramp tests for those whose diuretic dose were decreased. Black bar represents the first test and red bar represents the second test. CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure.

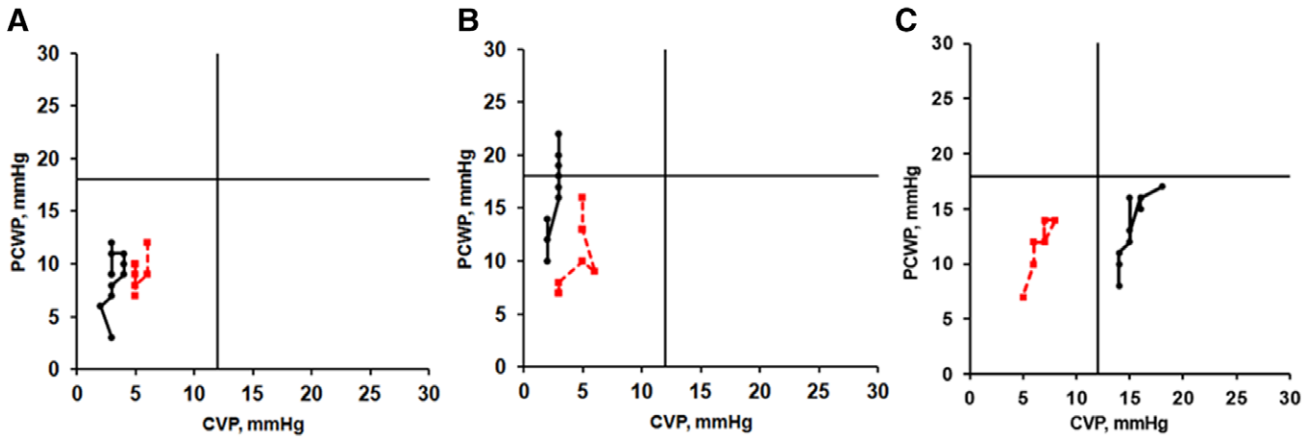

Figure 5. CVP–PCWP relationships of individual patients during the two speed ramp tests for those whose diuretic dose were increased. Black bar represents the first test and red bar represents the second test. CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure.

provide a patient-specific hemodynamic fingerprint. In addition, speed-dependent hemodynamics and echocardiographic changes (*i.e.*, slope of the respective relationships[12]) were also reproducible between the two time points. These findings were the same for patients implanted with a HeartMate II or an HVAD LVAD, for those with DT or bridge to transplant, and for those with ischemic or nonischemic etiology for their HF.

These fingerprints are relatively unique for each patient, and should be considered during long-term tailor made LVAD management for each patient. During daily monitoring, early detection of abnormality from the fingerprint may result in successful preventive therapy. We used invasive hemodynamic study for repeated monitoring, but noninvasive devices such as CardioMEMS may be alternative.[13]

Although the reason(s) why the LVAD RPM-dependent CVP–PCWP relationship appears to be relatively unique for a given patient remain(s) uncertain, we postulate that this relationship is determined by each patient's volume status, right and left ventricular contractility, and pulmonary and systemic vascular resistances. In addition, certain CVP–PCWP patterns, characterized by their position and slope on the CVP–PCWP plane may identify patients at risk for certain adverse conditions, such as right ventricular failure (due to either elevated pulmonary vascular resistance or intrinsic right ventricular dysfunction)[14] and fluid overload states with symptomatic HF. However, data obtained from a significant number of patients under well-characterized but different conditions will be required before such claims can be made.

Nevertheless, the present results demonstrating reproducibility and the nature of effects of diuretic dose changes on the CVP–PCWP relationship obtained in stable outpatients forms a strong foundation on which to build a more detailed understanding of the meaning of changes in this relationship.

Limitation

The main limitation of the present study is the small number of patients included from a single center. This limits statistical power to make definitive conclusions. Because speed ramp tests are not widely considered the standard of care and have not yet appeared as such in treatment guidelines,[9] the ability to perform this study at multiple centers is not yet possible. However, as more evidence builds regarding the utility and reliability of hemodynamic ramp tests and their potential to influence patient management, confirmatory results from multiple centers would strengthen the current conclusions. In the current study, we used repeated invasive hemodynamic test for assessment of hemodynamic ramp tests. However, chronically implanted devices such as CardioMEMS offer an attractive alternative. If such devices become more commonly used in LVAD patients, hemodynamic ramp tests could easily become part of routine follow-up. If such were to become the case, we should have as much understanding as possible of the behavior of these curves over time in stable patients and how they are modified by different pathologies. For the HVAD in particular, understanding of the relationship between HVAD waveform characteristics and LV filling pressure has the potential to make ramp tests more routine without the need for repeated catheterization.[13,15] The second speed ramp tests were performed a median of 454 days after LVAD implantation and 278 days following the first test. It would be important to confirm reproducibility of these hemodynamic data at even longer time points to test the degree to which long-term changes in patient physiology would modify the relationships studied.

Conclusions

Stable LVAD patients had relatively fixed though unique hemodynamic profiles when indexed by the RPM-dependent CVP–PCWP relationship over the course of a year. These curves shifted a small amount in response to changes in diuretic therapy, but maintained the same general form. Accordingly, these relationships appear to provide a patient-specific hemodynamic fingerprint. The current results provide the foundation for future research to determine whether different patterns of these relationships have any prognostic implications and whether deviations from a baseline test aid in diagnosis at times of clinical deterioration or device malfunction.

References

1. Slaughter MS, Rogers JG, Milano CA, *et al*; HeartMate II Investigators: Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 361: 2241–2251, 2009.

2. Aaronson KD, Slaughter MS, Miller LW, *et al*; HeartWare Ventricular Assist Device (HVAD) Bridge to Transplant ADVANCE Trial Investigators: Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. *Circulation* 125: 3191–3200, 2012.
3. Mehra MR, Naka Y, Uriel N, *et al*; MOMENTUM 3 Investigators: A fully magnetically levitated circulatory pump for advanced heart failure. *N Engl J Med* 376: 440–450, 2017.
4. Rogers JG, Pagani FD, Tatooles AJ, *et al*: Intrapericardial left ventricular assist device for advanced heart failure. *N Engl J Med* 376: 451–460, 2017.
5. Kirklin JK, Naftel DC, Pagani FD, *et al*: Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant* 34: 1495–1504, 2015.
6. Hasin T, Marmor Y, Kremers W, *et al*: Readmissions after implantation of axial flow left ventricular assist device. *J Am Coll Cardiol* 61: 153–163, 2013.
7. Maltais S, Kilic A, Nathan S, *et al*; PREVENT Study Investigators: PREVENtion of HeartMate II Pump Thrombosis Through Clinical Management: The PREVENT multi-center study. *J Heart Lung Transplant* 36: 1–12, 2017.
8. Smith EM, Franzwa J: Chronic outpatient management of patients with a left ventricular assist device. *J Thorac Dis* 7: 2112–2124, 2015.
9. Feldman D, Pamboukian SV, Teuteberg JJ, *et al*; International Society for Heart and Lung Transplantation: The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: Executive summary. *J Heart Lung Transplant* 32: 157–187, 2013.
10. Uriel N, Sayer G, Addetia K, *et al*: Hemodynamic ramp tests in patients with left ventricular assist devices. *JACC Heart Fail* 4: 208–217, 2016.
11. Nahumi N, Jorde U, Uriel N: Slope calculation for the LVAD ramp test. *J Am Coll Cardiol* 62: 2149–2150, 2013.
12. Jung MH, Gustafsson F, Houston B, Russell SD: Ramp study hemodynamics, functional capacity, and outcome in heart failure patients with continuous-flow left ventricular assist devices. *ASAIO J* 62: 442–446, 2016.
13. Abraham WT, Adamson PB, Bourge RC, *et al*; CHAMPION Trial Study Group: Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: A randomised controlled trial. *Lancet* 377: 658–666, 2011.
14. Lampert BC, Teuteberg JJ: Right ventricular failure after left ventricular assist devices. *J Heart Lung Transplant* 34: 1123–1130, 2015.
15. Reyes C, Voskoboynikov N, Chorpenning K, *et al*: Accuracy of the HVAD pump flow estimation algorithm. *ASAIO J* 62: 15–19, 2016.