ORIGINAL RESEARCH

Novel Left Heart Catheterization Ramp Protocol to Guide Hemodynamic Optimization in Patients Supported With Left Ventricular Assist Device Therapy

Andrew N. Rosenbaum, MD; Robert P. Frantz, MD; Sudhir S. Kushwaha, MD; John M. Stulak, MD; Simon Maltais, MD, PhD; Atta Behfar, MD, PhD

Background—Left ventricular (LV) hemodynamic assessment has been sparsely performed in patients supported on continuous-flow LV assist devices (cfLVADs). Insight into dynamic changes of left heart parameters during ramp studies may improve LV assist device optimization and evaluate pathology.

Methods and Results—To complement right heart catheterization, a novel technique for left heart catheterization in patients with a cfLVAD was developed. Patients implanted with cfLVADs underwent hemodynamic ramp left heart catheterization and right heart catheterization with transthoracic echocardiography. Continuous aortic and LV pressures were measured along with right atrial, pulmonary artery, and pulmonary capillary wedge pressures. A novel index, the transaortic gradient (TAG) was established. Thirty eight patients with cfLVADs were evaluated at a median of 446 days (interquartile range, 183–742) after device implant. During left heart catheterization performed for hemodynamic optimization, drop-in LV end-diastolic pressure and pulmonary capillary wedge pressure were associated with a rise in TAG. A range was identified for TAG (20–40 mm Hg) as providing the most optimal level of hemodynamic offloading. Pathologic states deviated from normal responses to ramp. LV assist device thrombosis was associated with an inability to increase in TAG during speed ramp. Significant aortic insufficiency was associated with a marked increase in LV end-diastolic pressure despite a concomitant decrease in pulmonary capillary wedge pressure with increasing LV assist device speeds.

Conclusions—Inclusion of left heart catheterization to a typical right heart catheterization LV assist device ramp protocol imparted unique insights to optimize cfLVAD speeds in different clinical scenarios. A novel index, the TAG was defined and provided additional resolution to optimized offloading. **(*J Am Heart Assoc*. 2019;8:e010232. DOI: 10.1161/JAHA.118.010232.)**

Key Words: catheterization • hemodynamics • left ventricular assist device • transaortic gradient

An emerging treatment of choice for refractory heart failure (HF), continuous-flow left ventricular (LV) assist devices (cfLVADs) have been implanted in over 15 000 patients as bridge-to-transplant or destination therapy.[1] Continued improvements in outcomes are driven by advancements in surgical technique, miniaturization of devices, anticoagulation and antiplatelet therapies, and management of device thrombosis or malfunction.[2] However, both optimization and evaluation of LV assist device (LVAD) performance pose significant clinical challenges caused by the unique hemodynamic paradigm inherent to continuous-flow devices.

To address this issue, novel strategies have been developed to understand the native heart-cfLVAD interaction. Echocardiography has been combined with incremental increases in LVAD speeds, termed a ramp study, to advance the understanding of continuous-flow hemodynamics.[3] Although ramp studies were originally utilized for diagnosis of LVAD thrombosis, the utility of these tests have been expanded to evaluation and management of LVAD speed optimization and valve disease via echocardiographic parameters.[4–6]

However, echocardiographic ramp studies are hampered by difficulty in consistently obtaining quality echocardiographic images.[4] Furthermore, echocardiographic ramp studies lack resolution for hemodynamic evaluation,[6] which may be exacerbated

---

From the Departments of Cardiovascular Diseases (A.N.R., R.P.F., S.S.K., A.B.) and Cardiovascular Surgery (J.M.S., S.M.), William J von Liebig Center for Transplantation and Clinical Regeneration (R.F., S.K., A.B.), and VanCleve Cardiac Regenerative Medicine Program, Center for Regenerative Medicine (A.B.), Mayo Clinic, Rochester, MN.

Accompanying Figure S1 and Videos S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010232

Correspondence to: Atta Behfar, MD, PhD, Mayo Clinic Rochester, 200 1st Street SW, Rochester, MN 55905. Email: behfar.atta@mayo.edu

Received September 12, 2018; accepted December 24, 2018.

Clinical Perspective

What Is New?

- Hemodynamics during left heart catheterization ramp study in patients supported on left ventricular (LV) assist device therapy have not been previously reported and results facilitate understanding of LV assist device–native circulation physiology.
- A novel index, the transaortic gradient, helps define LV offloading and correlated inversely with both markers of LV filling pressures and right ventricular systolic function.

What Are the Clinical Implications?

- Left heart catheterization ramp study may be able to further optimize LV assist device speed in patients supported on LV assist device therapy and provides useful data on certain pathologic states (ie, aortic regurgitation and pump thrombosis).

by differences in devices.[7] These observations fostered the development of the invasive ramp study via right heart catheterization (RHC). Despite genuine advancement, there have been limitations with prior data derived from invasive studies, including small sample sizes, lack of reproducibility, and use of indirect Fick measurements.[6] As such, no invasive ramp study has been able to show correlation between speed adjustments and clinical outcomes.[8]

Despite the advances in the understanding of cfLVAD physiology and hemodynamics, real-time evaluation of LV pressures and transaortic hemodynamics have yet to be evaluated under various loading conditions as determined with cfLVAD speed changes. The purpose of the current study is to describe a novel technique for left heart catheterization (LHC) in patients with cfLVADs, establishing a hemodynamic framework whereby LHC findings identify a unique zone of hemodynamics optimization based on the novel transaortic gradient (TAG) and LV end-diastolic pressure (LVEDP). The findings provided with this approach relate to a variety of device support scenarios.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Sample

The current study is a retrospective analysis of patients undergoing LHC/RHC ramp study at our institution. Patients included in the current study included those who had previously undergone cfLVAD implantation with a Heartmate II LVAD, Heartmate III LVAD (Abbott Laboratories), or HeartWare ventricular assist device (Medtronic Inc) and who underwent combined RHC and LHC between October 1, 2015, and March 15, 2018 (n=38). Various indications for LHC were present: 21 (55%) were performed for hemodynamic optimization, 7 (18%) were performed to evaluate aortic insufficiency (AI), 5 (13%) were performed to evaluate for pump thrombosis, 3 (8%) were performed to evaluate for device malfunction or alarms, and 2 (5%) were performed for consideration of weaning of mechanical circulatory support. The Mayo Clinic's institutional review board approved the current study. Requirement for informed consent was waived.

LHC and RHC

Invasive hemodynamic ramp studies were performed on full anticoagulation and antiplatelet therapies, although the recommendation is for an international normalized ratio goal of <3.0 at the time of the procedure. Patients with central coaptation stitch are not suitable for this evaluation as the left ventricle cannot be accessed. Percutaneous arterial access was obtained at the radial artery or brachial artery, both under ultrasound guidance (SonoSite S-ICU, FUJIFILM SonoSite, Inc). An exchange-length wire was bent to establish a 3-cm wide 90-degree bend to prevent accidental entrance into the LVAD inflow cannula upon LV cannulation. A 5F pigtail catheter with the exchange-length wire was brought to the aortic root under fluoroscopic guidance. Once at the aortic valve, the LVAD speed was decreased to allow opening of the aortic valve (as imaged by transthoracic echocardiogram) to facilitate passage into the left ventricle. An exchange-length wire was advanced via the pigtail into the left ventricle. Afterward, the pigtail catheter was removed and a 5F multipurpose guide was advanced over the wire into the left ventricle. The exchange-length wire was removed. A high-fidelity, micromanometer pressure wire (Aeris PressureWire, Abbott Laboratories) was introduced through the guide and placed in the left ventricle, inferior to the inflow cannula. The high-fidelity wire was calibrated to the fluid-filled catheter reading; transducers were zeroed at mid-axilla, measured by laser calipers. The guide catheter was then pulled back into the aorta to generate a simultaneous LV and aortic waveform. The LVAD was typically turned down to 200 to 400 rpm below the baseline speed for the Heartmate II and turned down by 60 to 100 rpm for the HeartWare. From there, increases in speed by 400 rpm (Heartmate II) and 100 rpm (HeartWare) were performed and the transaortic pressure gradient was obtained.

RHC was performed simultaneously. Baseline oxygen consumption was obtained using the Ultima Cpx Metabolic Stress Testing System (MGC Diagnostics C.), for accurate Fick

DOI: 10.1161/JAHA.118.010232

cardiac output calculations. Pulmonary artery and systemic arterial oxygen saturation values, as well as right atrial pressure (RAP), pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCWP) tracings, were obtained using a 7F fluid-filled catheter (single balloon wedge, Arrow International, Inc) and were recorded at each stage of the protocol. A representative setup during simultaneous LHC/RHC for patients supported on a Heartmate II and on a HeartWare are shown in Videos S1 and S2, respectively.

Device Thrombosis

Our approach to device thrombosis has been previously described.[9] Briefly, device thrombosis is suspected in patients with elevated markers of intravascular hemolysis, defined as greater than twice the baseline value, particularly a lactate dehydrogenase level >1000 U/L, with an elevated plasma-free hemoglobin level (>12 mg/dL) after excluding other causes of hemolysis. Additional necessary findings included either worsening HF or increases in LVAD power by ≥2 W. Confirmed device thrombosis was defined as the presence of thrombosis on the LVAD rotor upon device explant. All patients who met these criteria were admitted and placed on intravenous unfractionated heparin with a goal activated partial thromboplastin time of 50 to 70 seconds or anti-Xa level 0.3 to 0.7 unit/mL and had intensification of their antiplatelet regimen.

Aortic-LV Pressure Gradient (TAG)

A novel index to understand LV-aortic-cfLVAD hemodynamics is the TAG, which was defined as the peak-to-peak gradient between LV systolic pressure and aortic systolic pressure (Figure S1). This is performed with an end-expiratory breath hold to establish a consistent waveform. We attempted to define an optimal range for the TAG to associate with optimal LV hemodynamics and offloading.

Echocardiography

Simultaneous transthoracic echocardiography is performed to evaluate other parameters during the study. At baseline and each subsequent phase, including speed changes or medication changes, LV end-diastolic diameter in diastole, ventricular septal position, mitral regurgitation, qualitative right ventricular (RV) function, AI, and aortic valve opening were evaluated, if possible. AI was graded using techniques endorsed by the American Society of Echocardiography.[10] Echocardiography was not only used to optimize patients based on clinical guidelines and assist with the determination of adequate offloading but can be useful to capture suck-down events.

Optimization

At the conclusion of the LHC ramp protocol, we analyzed the TAG in combination with resting biventricular filling pressures and imaging characteristics to define the optimal LVAD speed. In each case, we attempted to find an LVAD speed that minimized biventricular filling pressures, avoided suck-down events at the inflow cannula, minimized AI if applicable, and maximized Fick-derived cardiac index (CI).

Statistical Analysis

Continuous variables are given as mean±SD unless otherwise stated. Categorical variables are given as number (percentage) unless otherwise stated. Comparison between continuous variables was performed using a Student *t* test when 2 groups were compared or ANOVA when greater than 2 groups. Sequential values were compared using a matched-pair *t* test. Categorical variables were compared using Fisher exact test. Linear regression analysis was used to evaluate associations between continuous variables. R^2 values represent the percent variability in the outcome data explained by the independent variable. All data analysis was performed using JMP 13.0 Pro (SAS Institute, Inc).

Results

Patient characteristics are described in the Table. Briefly, the median age of patients was 61 years (interquartile range, 50–66) and most patients were men (24 [63%]). The device distribution was 20 (53%) Heartmate II, 17 (45%) HeartWare, and 1 (3%) Heartmate III. LHC was performed at a mean of 513±384 days after implant.

Hemodynamic Optimization

A sample of an LHC hemodynamic tracing is shown in Figure 1, where a decrease in pulsatility of the LV and aortic waveforms with increasing cfLVAD speed is demonstrated; the TAG rises from 5 mm Hg at baseline to 45 mm Hg at the final speed.

The largest cohort of patients (n=21) underwent LHC/RHC to optimize hemodynamics. These patients had an average mean RAP of 13±5 mm Hg, mean PAP of 28±9 mm Hg, and mean PCWP of 15±4 mm Hg. The mean pulmonary vascular resistance of the cohort was 3.1±2.5 WU. These patients had a mean pulmonary artery pulsatility index of 2.1±1.0 and an RV stroke work index (RVSWI) of 527±232 mm Hg×mL/m^2. The mean CI was 2.6±0.7 L/min per m^2 and the mean LVEDP was 13±6 mm Hg. The mean TAG was 14±11 mm Hg initially. The mean arterial pressure (centrally measured) was 89±12 mm Hg at a heart rate of 75±15 beats per

Table. Baseline Characteristics of Patients With cfLVAD Undergoing LHC by Device

	Overall (n=38*)	Heartmate II (n=20)	HeartWare (n=17)	*P* Value
Age, y	59±10	64±10	54±9	0.002
Women, No. (%)	14 (37)	2 (10)	11 (65)	0.001
BMI, kg/m^2	28±7	29±5	26±8	0.17
Ischemic cause, No. (%)	15 (39)	11 (55)	4 (24)	0.09
Implant indication—BTT, No. %)	16 (43)	1 (5)	14 (88)	<0.001
INTERMACS score	2.6±1.0	2.7±1.0	2.5±1.0	0.72
Preimplant LVEDd, mm	69±10	70±10	69±11	0.76
Percent biventricular pacing/RV pacing/intrinsic rhythm, %	24/37/39	10/45/45	35/29/35	0.17
LVAD speed		9200±400	2660±160	···
Right heart catheterization				
Mean RAP, mm Hg	12±6	10±5	14±6	0.04
Mean PAP, mm Hg	26±9	22±7	30±11	0.02
Mean PCWP, mm Hg	14±6	13±6	16±6	0.15
PVR, WU	2.8±2.0	2.1±0.9	3.5±2.6	0.07
Cardiac index, L/min per m^2	2.4±0.6	2.4±0.4	2.4±0.8	0.85
MAP, mm Hg	85±11	84±8	86±13	0.76
HR, bpm	76±15	72±13	80±16	0.13
PAPi	2.1±1.2	2.5±1.3	1.9±0.9	0.14
RVSWI, Hg×mL/m^2	456±213	430±166	486±266	0.49

BMI indicates body mass index; bpm, beats per minute; BTT, bridge to transplant; cfLVAD, continuous-flow left ventricular assist device; HR, heart rate; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; LVEDd, left ventricular end-diastolic diameter in diastole; MAP, mean arterial pressure; PAP, pulmonary artery pressure; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricular; RVSWI, right ventricular stroke work index.

*One patient with the Heartmate II device was included in the overall analysis (first column) but not described elsewhere in the table.

minute. After speed adjustments, the right heart filling pressures were largely unchanged (mean RAP 12±5 mm Hg, mean PAP 27±9 mm Hg, and mean PCWP 14±5 mm Hg). LVEDP was also unchanged (12±6 mm Hg). There was a rise in the TAG to 20±13 mm Hg. For patients who required speed adjustments, the patients with a Heartmate II were increased, on average, from 9300 to 9700 rpm and the patients with a HeartWare were increased, on average, from 2620 to 2720 rpm. The single patient with a Heartmate III was increased from 5700 to 5800 rpm.

Evaluation of Hemodynamics

Hemodynamics over the LHC/RHC ramp studies were evaluated to understand biventricular hemodynamics in relation to optimization in the cohort above, as these patients had no suggestion of pathology before the ramp study.

The relationship between parameters of offloading (PCWP, LVEDP, and TAG) and LVAD speeds was evaluated over a clinical range of Heartmate II and HeartWare speeds (Figure 2). In patients with a Heartmate II, there was an association between LVEDP and RPM (R^2=0.08, P=0.02), as well as PCWP and RPM (R^2=0.21, P=0.001) (Figure 2, left panels). In patients supported on a HeartWare device, PCWP and LVEDP correlated with RPM (PCWP: R^2=0.18, P=0.0003; LVEDP: R^2=0.10, P=0.005) (Figure 2, right panels). For both pump types, TAG correlated significantly with RPM (Heartmate II: R^2=0.36, P<0.001; HeartWare: R^2=0.09, P=0.007).

Figure 3 shows the relationship between parameters of offloading (LVEDP and PCWP) and TAG as well as parameters of RV function (RV stroke work index and pulmonary artery pulsatility index) and TAG. There were modest yet statistically significant inverse correlations observed between each variable and the TAG. Additionally, while there were significant inverse correlations between CI assessed by direct Fick measurement and PCWP and LVEDP (R^2=0.11, P=0.003 for both), there was no association between TAG and CI (R^2=0.0008, P=0.80).

To delineate a reproducible target for optimization, TAG was evaluated against a normalized LVEDP, avoidance of excessive LV “suck-down,” RV function, and CI, while operating at a recommended speed. Appropriate offloading, defined as an

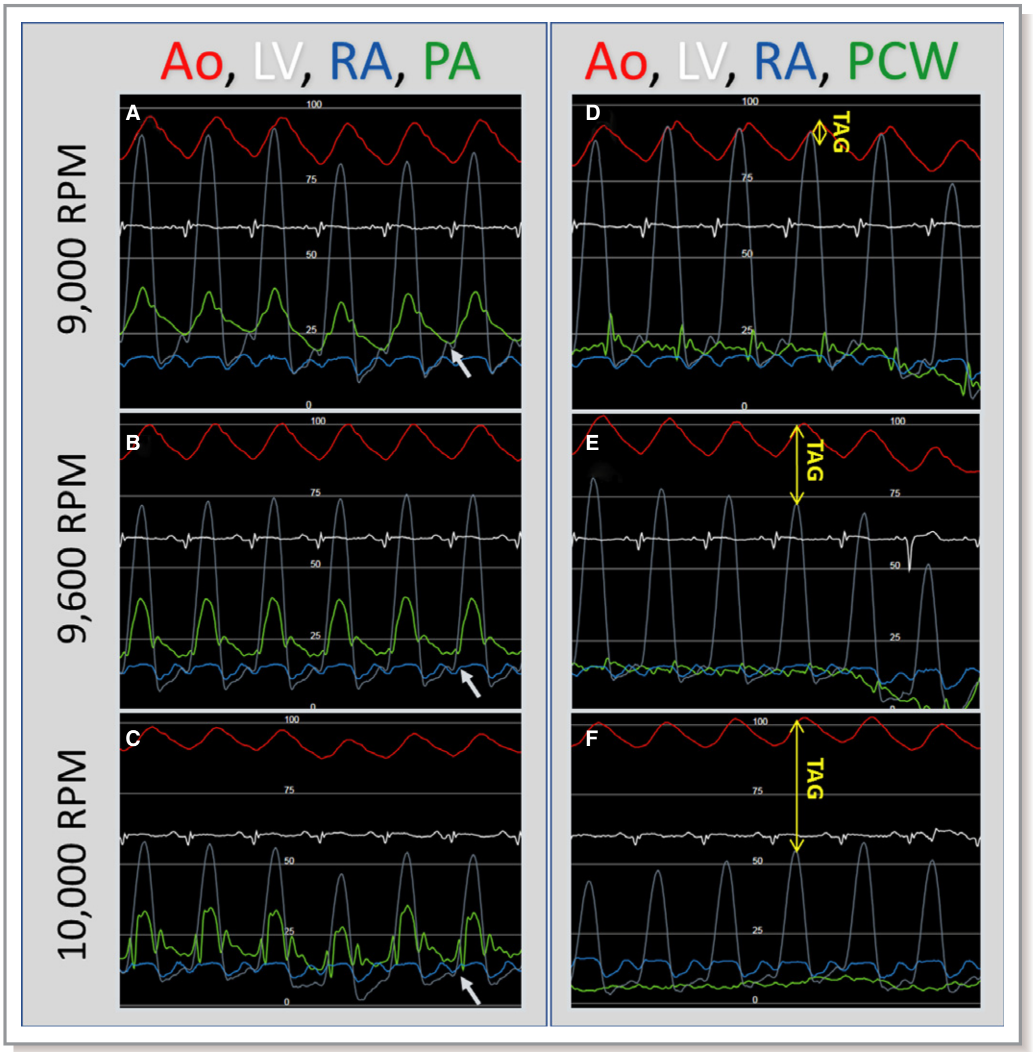

Figure 1. Example of left heart catheterization left ventricular assist device ramp study. Simultaneous monitoring of aortic pressure (Ao, red), left ventricular pressure (LV, grey), and right atrial pressure (RA, blue) along with (**A** through **C**) pulmonary artery pressure (green) or (**D** through **F**) pulmonary capillary wedge pressure (PCW, green) waveforms are shown. With increasing speeds (from top panels to bottom) an accentuation of transaortic gradient (TAG; yellow) is noted corresponding with reduction in left ventricular end-diastolic pressure (arrows) and PCW.

LVEDP <16 mm Hg was obtained generally at TAG values of ≥20 mm Hg. In contrast, TAG values >40 mm Hg resulted in decrements in RV stroke work index and pulmonary artery pulsatility index (<400–450 mm Hg×mL/m^2 and <2, respectively). Thus, the optimal TAG range was defined at 20 to 40 mm Hg (Figure 4A through 4C). A graphical plot of TAG against LVEDP defined additional zones (Figure 4A through 4C) correlating with clinical diagnosis including volume overload or significant AI (TAG between 20 and 40 mm Hg with LVEDP >16 mm Hg), pump thrombosis or severe fluid overload (TAG <20 mm Hg and LVEDP >16 mm Hg), excessive pump speed (TAG >40 mm Hg), and various conditions resulting in low LV volume including LV recovery or dehydrated status (TAG <20 mm Hg and LVEDP <16 mm Hg).

Establishment of these criteria resulted in reclassification of optimization status. Using previously defined criteria, 38% of the stages evaluated would have met prior optimization criteria (RAP <12 mm Hg and PCWP <16 mm Hg), whereas only 13% of stages met criteria for optimal offloading (20 mm Hg < TAG <40 mm Hg and LVEDP <16 mm Hg), suggesting a narrower band of optimization.

LVAD Thrombosis

Five patients were evaluated for LVAD thrombosis. Each presented with an elevated lactate dehydrogenase level (mean 1070 U/L) and 1 had power spikes just before admission. Baseline hemodynamic parameters were defined

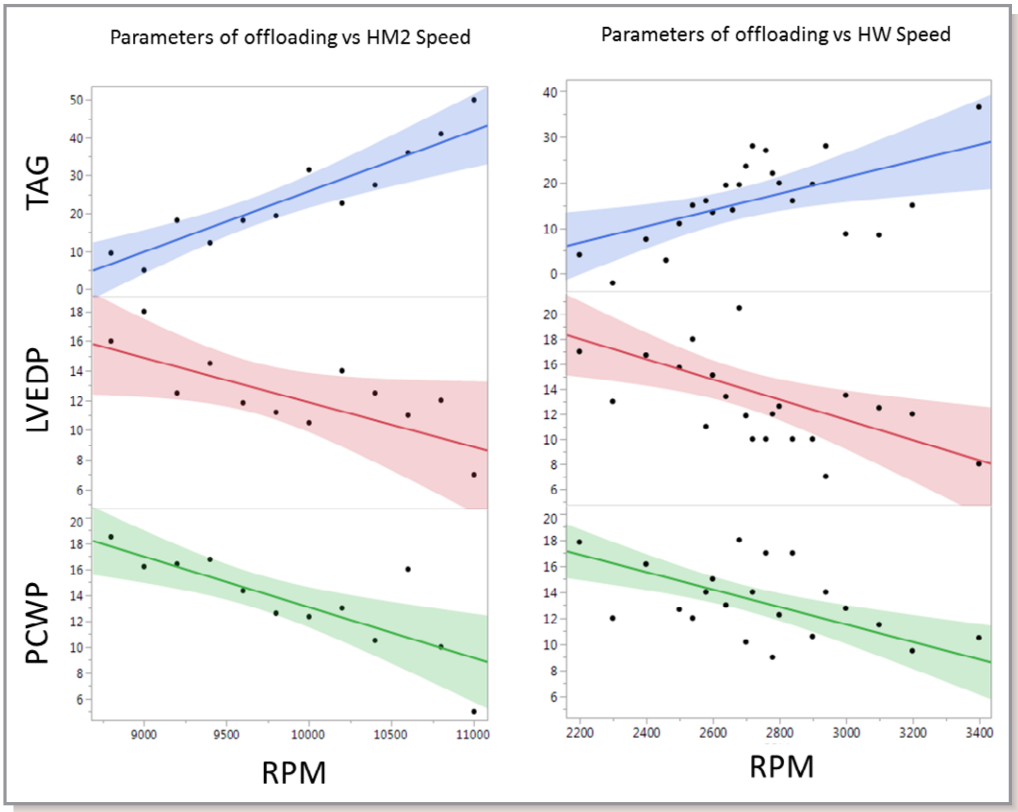

Figure 2. Values of transaortic gradient (TAG), pulmonary capillary wedge pressure (PCWP), and left ventricular end-diastolic pressure (LVEDP) plotted over a range of clinical continuous-flow left ventricular assist device speeds. In patients with a HeartMate II (HM2), LVEDP and PCWP were associated with changes in revolutions per minute (RPMs; R^2=0.08 [P=0.02] and R^2=0.21 [P=0.001], respectively). In patients with a HeartWare (HW) ventricular assist device, PCWP and LVEDP correlated with RPMs (R^2=0.18 [P=0.0003] and R^2=0.10 [P=0.005], respectively). For both pump types, TAG correlated significantly with RPMs (HM2: R^2=0.36 [P<0.001] and HW: R^2=0.09 [P=0.007]). Shaded areas indicate CIs.

for this cohort: mean RAP 11±7, mean PAP 18±8 mm Hg, and mean PCWP 15±8 mm Hg. CI was acceptable, with a mean value of 2.5±0.4 L/min per m^2. LVEDP was 12±5 mm Hg and baseline TAG was 16±15 mm Hg.

Notably, patients had markedly different responses to increasing LVAD speed. As an example, 1 patient had a baseline TAG of 2 mm Hg at 8800 rpm, and the final gradient was 1 mm Hg at 10 000 rpm. The patient continued to have refractory hemolysis despite enhanced anticoagulation and was found to have confirmed device thrombosis upon device exchange. In contrast, the other nonobstructed patients saw a brisk rise in their TAGs to an average of 47 mm Hg at highest achieved speed, suggesting no compromise in pump function from thrombus or obstruction. These findings are shown in Figure 4B.

Aortic Insufficiency

The cohort of patients (n=7) who underwent LHC for AI had elevated filling pressures at baseline speed (mean RAP 15±7, mean PAP 30±10 mm Hg, and mean PCWP 18±7 mm Hg). The resting CI was impaired at 1.9±0.3 L/min per m^2. The baseline LVEDP was 17±3 mm Hg and the TAG was 21±14 mm Hg. At baseline, guideline-based echocardiographic assessment of AI had been performed. Using these criteria, grades of AI were described as moderate in 5 patients and mild to moderate in 2 patients. Importantly, in most patients, both an increase in TAG and a decrease in LVEDP (down to 17±4 mm Hg) could be attained (Figure 4C). However, in 1 patient with severe exertional symptoms but an echocardiographically determined moderate AI (vena contracta of 4 mm), a rapid increase in LVEDP was noted with modest speed increase despite a lack of change in PCWP, identifying a slower speed as the most optimal setting (Figure 4C and 4D).

We then evaluated the correlations between PCWP and LVEDP. As expected, in patients being evaluated solely for hemodynamic optimization, we found a strong correlation between PCWP and LVEDP (R^2=0.45, P<0.0001) (Figure 5A). However, there was no significant association between PCWP

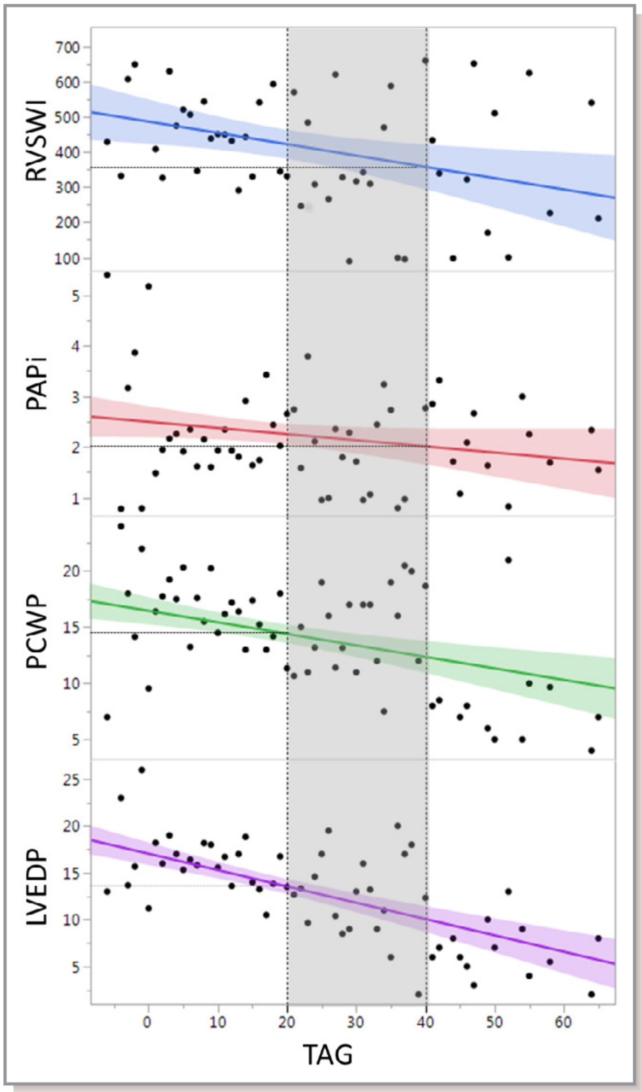

Figure 3. Indices of offloading and right ventricular (RV) function by transaortic gradient (TAG) during ramp study. Pulmonary artery pulsatility index (PAPi), RV stroke work index (RVSWI), pulmonary capillary wedge pressure (PCWP), and left ventricular end-diastolic pressure (LVEDP) were evaluated over the course of the ramp study for multiple patients. Both markers of RV function showed an inverse relationship with TAG (RVSWI: R^2=0.10 [P=0.001] and PAPi: R^2=0.03 [P=0.03]). Both markers of offloading showed an inverse relationship with TAG as well (PCWP: R^2=0.10 [P<0.0001] and LVEDP: R^2=0.26 [P<0.0001]). Color-shaded areas indicate CIs. Grey shaded region represents hypothetical optimal zone.

and LVEDP in patients undergoing LHC for assessment of AI (R^2=0.001, P=0.87) (Figure 5B).

LVAD Weaning

Two patients underwent unique protocols to examine hemodynamics on decreasing or minimal support for consideration of weaning from permanent mechanical circulatory support. Filling pressures were normal at baseline in this cohort (mean pressures: RAP 6±2 mm Hg, PAP 16±4 mm Hg, PCWP 7±5 mm Hg, LVEDP 6±0 mm Hg). CI was 2.5±0.4 L/min per m^2.

In one example, the patient was brought to the laboratory and normal hemodynamics were observed at rest: baseline LVAD speed was 9000 rpm, RAP was 4 mm Hg, LVEDP was 6 mm Hg, CI was 2.22 L/min per m^2, and TAG was 14 mm Hg. LVAD speeds were decreased gradually to 7000 rpm temporarily. At that speed, RAP remained at 7 mm Hg, LVEDP rose to 13 mm Hg, and TAG fell to −6 mm Hg. A supine cycle ergometer was introduced and at 40 W of exercise, the patient had relatively preserved filling pressures (mean RAP 12 mm Hg, mean PAP 28 mm Hg, LVEDP 17 mm Hg). The TAG also remained at −3 mm Hg with an augmented cardiac output to 7.85 L/min, suggesting adequate native cardiac output reserve.

Complications of LHC

There are several theoretical complications of LHC in patients with cfLVAD (wire fracture within the inflow cannula with potential for embolization, damage to the aortic valve, aortic perforation or dissection, myocardial infarction, stroke, arterial dissection, or major or minor bleeding). In the current cohort, the only complications observed were minor bleeding following sheath removal in 4 of 38 (11%) patients; however, only 1 of these was related to the arterial sheath (3%), which was a small hematoma.

Echocardiographic Findings

In patients undergoing ramp study for hemodynamic optimization (n=21), the mean pre-LHC LV end-diastolic diameter was 59±10 mm, but study resulted in a negligible change in mean LV end-diastolic diameter (−0.33 mm, P=0.80). Aortic valve opening was present in 48% (n=10) of the cohort before LHC ramp study, and 2 patients had less aortic valve opening while 1 patient had more aortic valve opening after optimization. The ventricular septum was neutral in 19 of 21 (90%) patients in which it was evaluated, leftward in 2 of 21 (10%) patients, and rightward in 2 of 21 (10%) patients. However, echocardiography only identified one true change in septal position despite relatively large hemodynamic changes across the ramp study.

Discussion

We describe the first series of combined simultaneous RHC and LHC with ramp study in patients supported on cfLVAD

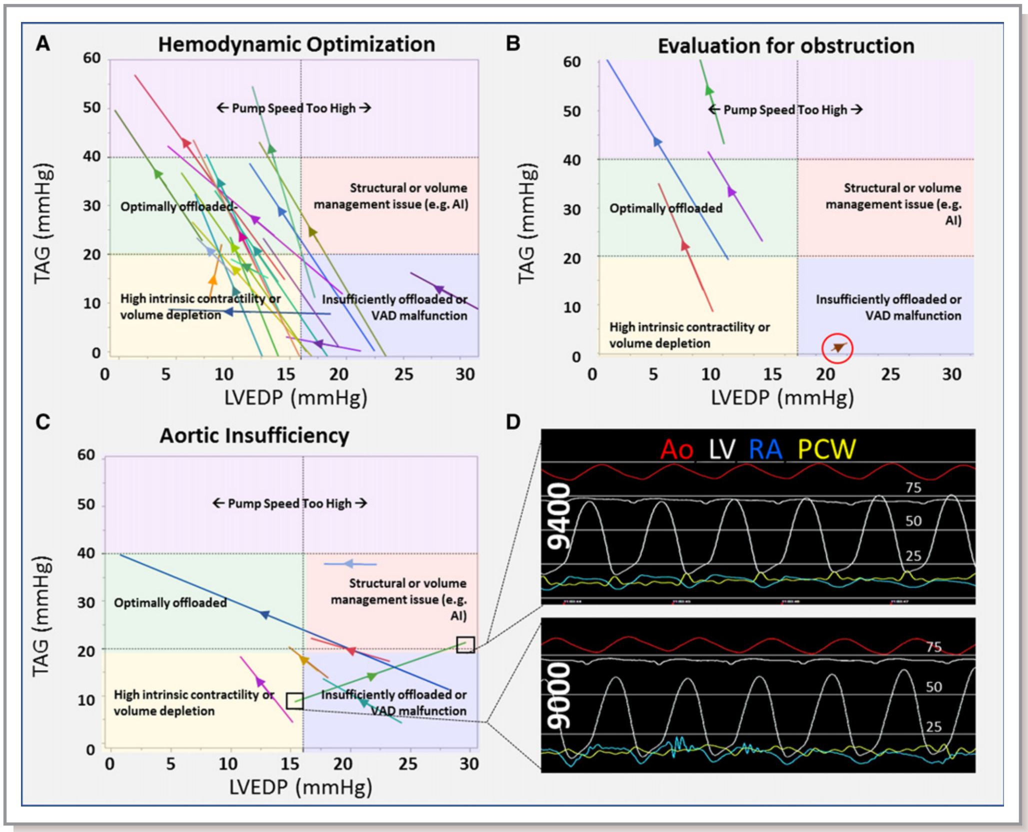

Figure 4. Hemodynamic evaluation of patients supported on left ventricular (LV) assist device (LVAD) therapy by left heart catheterization. Underlying clinical question for which the patients underwent right and left heart catheterization (**A**) hemodynamic optimization, (**B**) evaluation of thrombus or obstruction, and (**C**) evaluation of aortic insufficiency. Highlighted with the red circle in (**B**) is a patient in whom LVAD thrombosis was diagnosed, resulting in LVAD exchange; there is a clear lack of augmentation of the transaortic gradient (TAG) on speed increase. Highlighted with the green arrow in (**C**) is a patient with severe aortic insufficiency. The slope of the TAG/LV end-diastolic pressure (LVEDP) line is nearly orthogonal to patients in whom aortic insufficiency was milder. **D**, Right and left heart catheterization LVAD ramp study with simultaneous monitoring of aortic (Ao; red), LV (grey), right atrial (RA; blue), and pulmonary capillary wedge (PCW; green) pressure waveforms highlight divergence in LVEDP (rise) and pulmonary capillary wedge pressure (PCWP; fall) during LVAD speed increase in a patient with severe aortic insufficiency. VAD indicates ventricular assist device.

therapy. The utility of the TAG and LVEDP, obtained via LHC, is shown and provides significant additive resolution to the data that RHC ramp studies and transthoracic echocardiography provide. To this end, a zone of hemodynamic optimization, termed "Goldilocks zone" was defined herein utilizing LVEDP and TAG. Furthermore, the safety and feasibility of performing LHC catheterization in the LVAD-supported population was demonstrated without any significant adverse events.

Hemodynamic Optimization

Hemodynamic optimization continues to be a challenge in the management of patients with cfLVADs.[11–13] Current data and guidelines support evaluation of numerous end points for optimization, which may be mutually exclusive in certain patients and include normalization of filling pressures, establishment of a neutral septal position, intermittent aortic valve opening, adequate cardiac output, and, most importantly, relief of exertional dyspnea.[14,15] Recent reviews of management of patients with cfLVADs describes not only the difficulty in evaluating the degree of LV offloading but also the difficulty in balancing LV offloading without altering RV geometry to impair filling.[13,15] However, we believe that simultaneous use of LHC and RHC avoids this difficulty by evaluating biventricular function in relation to LVAD speed, allowing the ability to tune LVAD speed at an optimum setting.

LVAD Physiology and the TAG

Diagrammatic representation of pressure volume loops in the left ventricle under various cfLVAD speeds is provided to

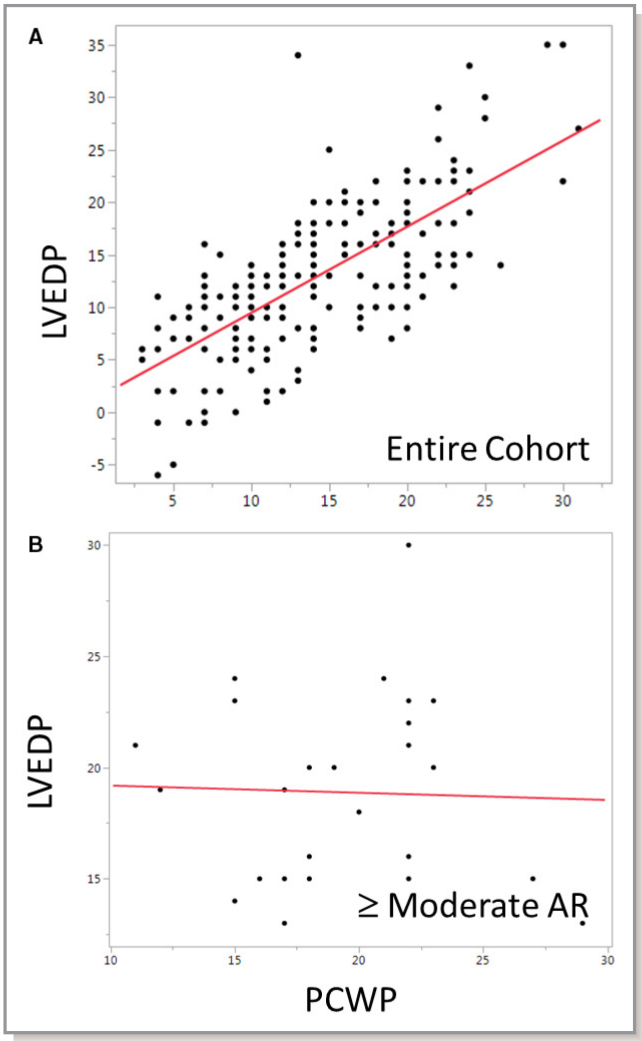

Figure 5. Association between left ventricular end-diastolic pressure (LVEDP) and pulmonary capillary wedge pressure (PCWP) during left ventricular assist device ramp studies. **A**, Linear correlation of LVEDP plotted against PCWP at each hemodynamic point (R^2=0.45, P<0.001). **B**, Linear correlation between LVEDP and PCWP in patients with at least moderate aortic regurgitation (AR) by transthoracic echocardiogram (R^2=0.001, P=0.87).

highlight the mechanistic basis for TAG changes with a cfLVAD speed ramp (Figure 6). In patients supported on cfLVADs, there is continuous volume removal from the left ventricle throughout the cardiac cycle. As a result, isovolumic relaxation and contraction times are eliminated, creating a triangular shape to the pressure volume loop. As the LVAD speed and flow are increased, a decrease in both preload and afterload of the left ventricle are observed, resulting in a decrement of both the LV stroke work and the peak LV pressure. The end result is the abolishment of pulsatility in the aortic waveform and an increasing dissociation between the aortic pressure and LV pressure as the LVAD device takes on an increasing role of pressurizing the systemic circulation.

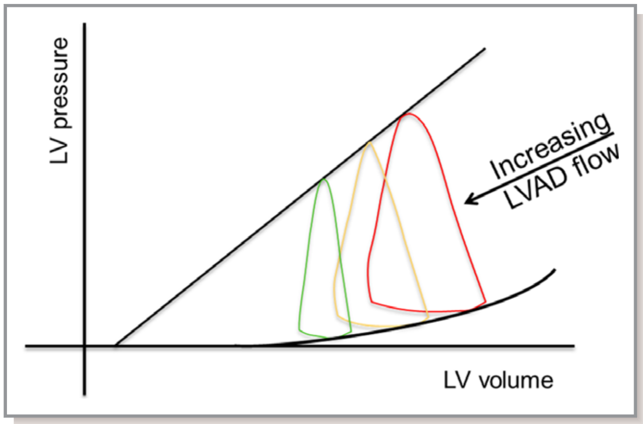

Figure 6. Diagrammatic representation of pressure-volume relationship in the left ventricle on left ventricular (LV) assist device (LVAD) support. With increasing LVAD speed in a normally functioning circuit, a more triangular conformation of the pressure-volume relationship is seen and LV stroke work as well as LV peak pressure in systole declines.

TAG likely represents a complex hemodynamics interplay of the left ventricle (offloading, native contractility), as well as the VAD flow; numerically it is the difference between the peak systolic pressure of the aorta and peak systolic pressure of the left ventricle. TAG provides a measurement that is proportional to the pump differential pressure (instantaneous aortic−LV pressure) and related to LV load.[16] The TAG, therefore, represents a more reliable marker of true LVAD offloading, and a low TAG at baseline may identify inadequate LV unloading by the cfLVAD independently of LVEDP or PCWP findings. Furthermore, TAG is noted to be much better associated with speed changes, suggesting it is the most sensitive parameter to assess offloading. In the majority of patients, an increase in LVAD rpm results in an increase in TAG and a decrease in LVEDP (Figures 2 and 4A). Separately, an inability to augment the TAG with speed ramp may signal a dysfunctional LVAD circuit (eg, rotor thrombus, cannula thrombus, severe kinking, and LVAD malfunction), providing a more definitive assessment upon which to decide about necessity of exchange. While a decrement in TAG could occur over time as a result of increased native cardiac contractility due to reverse remodeling, the presence of an elevated LVEDP (Figure 3) in tandem with symptomatic HF would suggest inadequate unloading.

However, the effect of unloading of the left ventricle via increasing pump speed may have various effects on the right ventricle.[17–20] While increased LV unloading results in reduced PCWP and decreasing pulmonary circulation resistance, it may have deleterious effects on RV function. First, negative pressure within the LV cavity in systole may induce a conformational change in the right ventricle that may impair septal contribution to RV systolic function. Second, increased LVAD flow may result in volume loading of the right ventricle, which has been shown to exhibit impaired adaptation to load over time in patients supported on LVAD therapy.[21]

In our experience, a TAG between 20 and 40 mm Hg and an LVEDP <16 mm Hg, results in optimal hemodynamics in the catheterization laboratory. Theoretically, the optimal TAG should be associated with the greatest CI as LVAD flows are generally higher with greater LVAD speeds until increasing afterload diminishes flow, as suggested by H-Q curves,[16,22] or the RV cannot accommodate increased load. Nevertheless, clinical outcomes related to achieving this threshold have yet to be ascertained and should be a focus of ongoing work. Previously, however, improvements in hemodynamics as a result of ramp studies were associated with improved quality of life and functional capacity.[23]

Simultaneous Transthoracic Echocardiography

We were unable to determine any specific echocardiographic markers that corresponded well with the hemodynamic pressure waveform tracings observed in the acute setting. Ventricular septal position was relatively insensitive for even significant changes in LV offloading. Echocardiography provided valuable data about aortic valve opening, mitral regurgitation, suck-down, and LV dimensions and provides a resource to monitor the long-term structural impact of hemodynamic optimization.

Clinical Utility and Role for LHC During LVAD Ramp Studies

Our preliminary results are insufficient to determine the precise role for the LHC ramp study in the routine evaluation of a patient with an LVAD. However, we believe that these data create a foundation on which to build an understanding of LV hemodynamics in patients supported with LVAD therapy, both for optimization and pathologic states. Specific areas of potential research interest going forward include:

1. Initial LVAD optimization postimplant.
2. Evaluating the extent of aortic regurgitation when guidelines and potential novel noninvasive indices are insufficient.[4,23]
3. Evaluating pump thrombosis when the intensive antiplatelet and anticoagulation regimen has not improved markers of hemolysis and clinical concern persists.
4. Evaluating patients for weaning from permanent mechanical support.[24]

Limitations

The present study is a retrospective analysis of a cohort of patients undergoing complex hemodynamic RHC and LHC at our institution for thorough evaluation of hemodynamics, which may result in a sampling bias. Patients with coagulopathies, sutured aortic valves, or lost to follow-up may be among those who did not undergo an LHC. The purpose of this study was to illustrate safety, feasibility, and utilization of this novel technique and to describe a systematic way in which it can be applied. Definitive conclusions cannot be drawn from the hemodynamic values obtained here, and the results shown are purely hypothesis-generating. However, this work creates a framework by which to derive future knowledge on hemodynamics in patients supported on cfLVADs and does provide initial evidence for utility in the evaluation and diagnosis of patients supported by durable continuous-flow devices. Additionally, the hemodynamics in the current study were not acquired in a blinded fashion per se but these are objective data and the initial clinical protocols were refined over the course of the study. Last, the hemodynamics including afterload were not actively manipulated during the study with volume or medications, limiting our observations to the impact of LVAD RPM. Beyond TAG and LVAD RPM assessment, future studies that manipulate preload, LV filling pressure, LV afterload, and RV afterload as key mediators of LVAD hemodynamics are warranted.

Conclusions

A novel technique for the hemodynamic evaluation of patients supported on durable cfLVADs is described. While the invasive nature of the diagnostic study precludes universal application in this cohort of patients, there may be specific indications for utilization of LHC in patients with cfLVADs, providing incremental data to assist the HF clinician with critical decision-making in selected scenarios. Future research should focus on the evaluation of LHC hemodynamics in a standardized way to establish thresholds useful to the advanced HF clinician.

Sources of Funding

Behfar is supported by grants from the National Institutes of Health, Van Cleve Cardiac Regenerative Medicine Program, Marriott Foundation, Michael S. and Mary Sue Shannon Family, and Florida Heart Research Institute.

Disclosures

A.N.R., R.P.F., S.S.K., J.M.S., and S.M. have no financial relationships or other conflicts of interest to disclose. A.B. is a co-founder of Rion, LLC and RioCOR, Inc. He has received grant funding and serves on the scientific advisory board for SmartPharm Therapeutics, Inc.

References

1. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB. Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant*. 2015;34:1495–1504.
2. Lampropulos JF, Kim N, Wang Y, Desai MM, Barreto-Filho JA, Dodson JA, Dries DL, Mangi AA, Krumholz HM. Trends in left ventricular assist device use and outcomes among Medicare beneficiaries, 2004–2011. *Open Heart*. 2014;1: e000109.
3. Uriel N, Morrison KA, Garan AR, Kato TS, Yuzefpolskaya M, Latif F, Restaino SW, Mancini DM, Flannery M, Takayama H, John R, Colombo PC, Naka Y, Jorde UP. 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;60:1764–1775.
4. Estep JD, Vivo RP, Krim SR, Cordero-Reyes AM, Elias B, Loebe M, Bruckner BA, Bhimaraj A, Trachtenberg BH, Ashrith G, Torre-Amione G, Nagueh SF. Echocardiographic evaluation of hemodynamics in patients with systolic heart failure supported by a continuous-flow LVAD. *J Am Coll Cardiol*. 2014;64:1231–1241.
5. Grinstein J, Kruse E, Sayer G, Fedson S, Kim GH, Sarswat N, Adatya S, Ota T, Jeevanandam V, Mor-Avi V, Lang RM, Uriel N. Novel echocardiographic parameters of aortic insufficiency in continuous-flow left ventricular assist devices and clinical outcome. *J Heart Lung Transplant*. 2016;35:976–985.
6. Uriel N, Sayer G, Addetia K, Fedson S, Kim GH, Rodgers D, Kruse E, Collins K, Adatya S, Sarswat N, Jorde UP, Juricek C, Ota T, Jeevanandam V, Burkhoff D, Lang RM. Hemodynamic ramp tests in patients with left ventricular assist devices. *JACC Heart Fail*. 2016;4:208–217.
7. Uriel N, Levin AP, Sayer GT, Mody KP, Thomas SS, Adatya S, Yuzefpolskaya M, Garan AR, Breskin A, Takayama H, Colombo PC, Naka Y, Burkhoff D, Jorde UP. Left ventricular decompression during speed optimization ramps in patients supported by continuous-flow left ventricular assist devices: device-specific performance characteristics and impact on diagnostic algorithms. *J Card Fail*. 2015;21:785–791.
8. Burkhoff D, Sayer G, Doshi D, Uriel N. Hemodynamics of mechanical circulatory support. *J Am Coll Cardiol*. 2015;66:2663–2674.
9. Fine NM, Topilsky Y, Oh JK, Hasin T, Kushwaha SS, Daly RC, Joyce LD, Stulak JM, Pereira NL, Boilson BA, Clavell AL, Edwards BS, Park SJ. Role of echocardiography in patients with intravascular hemolysis due to suspected continuous-flow LVAD thrombosis. *JACC Cardiovasc Imaging*. 2013;6:1129–1140.
10. Stainback RF, Estep JD, Agler DA, Birks EJ, Bremer M, Hung J, Kirkpatrick JN, Rogers JG, Shah NR. Echocardiography in the management of patients with left ventricular assist devices: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2015;28:853–909.
11. Chung BB, Sayer G, Uriel N. Mechanical circulatory support devices: methods to optimize hemodynamics during use. *Expert Rev Med Devices*. 2017;14:343–353.
12. Morley D, Litwak K, Ferber P, Spence P, Dowling R, Meyns B, Griffith B, Burkhoff D. Hemodynamic effects of partial ventricular support in chronic heart failure: results of simulation validated with in vivo data. *J Thorac Cardiovasc Surg*. 2007;133:21–28.
13. Lampert BC, Teuteberg JJ. Right ventricular failure after left ventricular assist devices. *J Heart Lung Transplant*. 2015;34:1123–1130.
14. Feldman D, Pamboukian SV, Teuteberg JJ, Birks E, Lietz K, Moore SA, Morgan JA, Arabia F, Bauman ME, Buchholz HW, Eng M, Dickstein ML, El-Banayosy A, Elliot T, Goldstein DJ, Grady KL, Jones K, Hryniewicz K, John R, Kaan A, Kusne S, Loebe M, Massicotte MP, Moazami N, Mohacsi P, Mooney M, Nelson T, Pagani F, Perry W, Potapov EV, Eduardo Rame J, Russell SD, Sorensen EN, Sun B, Strueber M, Mangi AA, Petty MG, Rogers J, Rowe AW. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. *J Heart Lung Transplant*. 2013;32:157–187.
15. Slaughter MS, Pagani FD, Rogers JG, Miller LW, Sun B, Russell SD, Starling RC, Chen L, Boyle AJ, Chillcott S, Adamson RM, Blood MS, Camacho MT, Idrissi KA, Petty M, Sobieski M, Wright S, Myers TJ, Farrar DJ. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. *J Heart Lung Transplant*. 2010;29:S1–S39.
16. Lim HS, Howell N, Ranasinghe A. The physiology of continuous flow left ventricular assist devices. *J Card Fail*. 2016;23:169–180.
17. Kang G, Ha R, Banerjee D. Pulmonary artery pulsatility index predicts right ventricular failure after left ventricular assist device implantation. *J Heart Lung Transplant*. 2016;35:67–73.
18. Morgan JA, Paone G, Nemeh HW, Murthy R, Williams CT, Lanfear DE, Tita C, Brewer RJ. Impact of continuous-flow left ventricular assist device support on right ventricular function. *J Heart Lung Transplant*. 2013;32:398–403.
19. Ochiai Y, McCarthy PM, Smedira NG, Banbury MK, Navia JL, Feng J, Hsu AP, Yeager ML, Buda T, Hoercher KJ, Howard MW, Takagaki M, Doi K, Fukamachi K. Predictors of severe right ventricular failure after implantable left ventricular assist device insertion: analysis of 245 patients. *Circulation*. 2002;106:I198–I202.
20. Dandel M, Potapov E, Krabatsch T, Stepanenko A, Löw A, Vierecke J, Knosalla C, Hetzer R. Load dependency of right ventricular performance is a major factor to be considered in decision making before ventricular assist device implantation. *Circulation*. 2013;128:14–24.
21. Houston BA, Kalathiya RJ, Hsu S, Loungani R, Davis ME, Coffin ST, Haglund N, Maltais S, Keebler ME, Leary PJ, Judge DP, Stevens GR, Rickard J, Sciortino CM, Whitman GJ, Shah AS, Russell SD, Tedford RJ. Right ventricular afterload sensitivity dramatically increases after left ventricular assist device implantation: a multi-center hemodynamic analysis. *J Heart Lung Transplant*. 2016;35:868–876.
22. Rich JD, Burkhoff D. HVAD flow waveform morphologies. *ASAIO J*. 2017;63:526–535.
23. 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*. 2016;62:442–446.
24. Segan L, Nanayakkara S, Vizi D, Mariani J, Kaye D. Exercise haemodynamics as a predictor of myocardial recovery in LVAD patients. *ASAIO J*. 2016;25:S108.

Supplemental Material

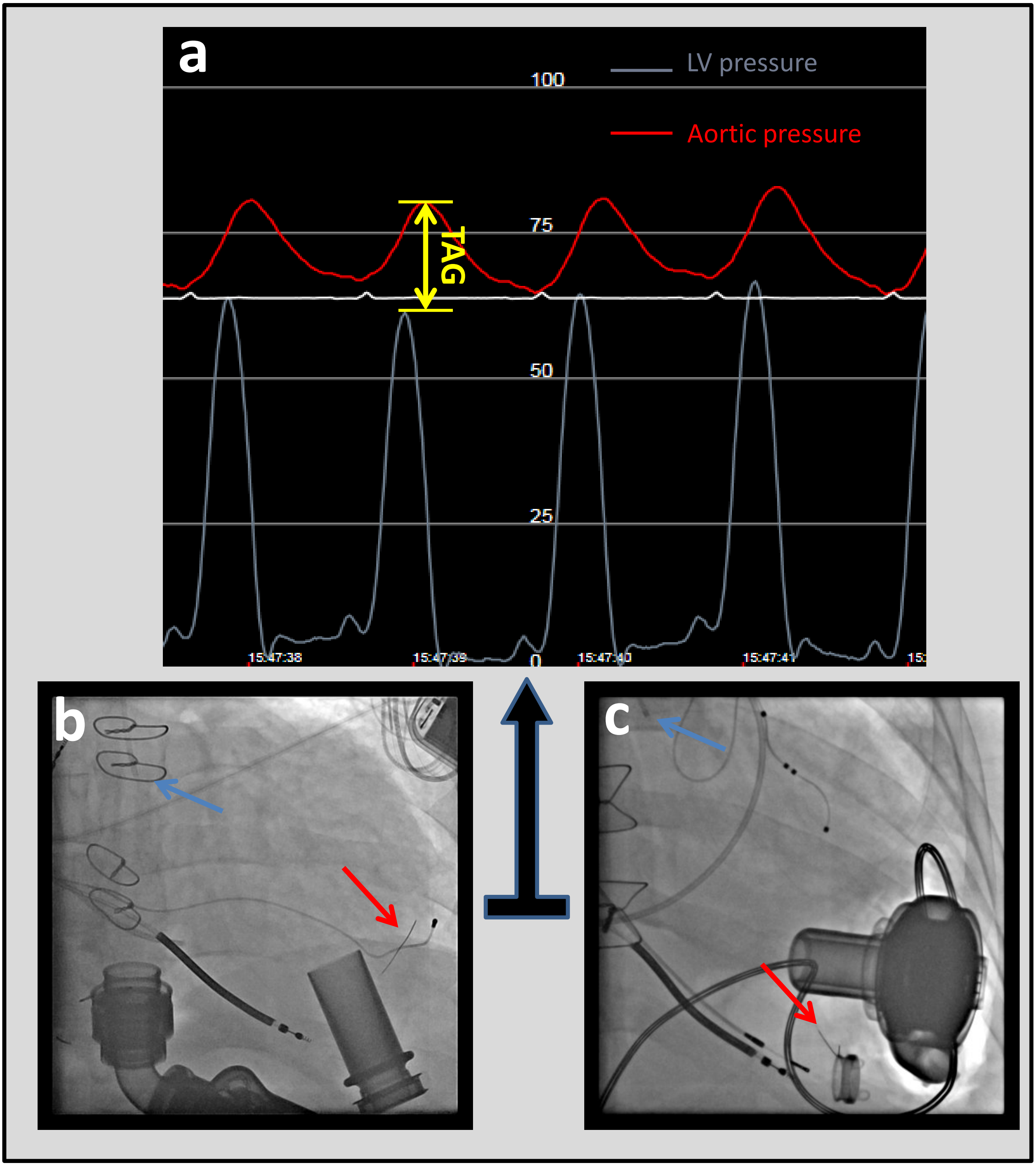

Figure S1. Depiction of the novel trans-aortic gradient (TAG) (a). Grey tracing represents left ventricular (LV) pressure and red tracing represents aortic pressure. Cinefluoroscopic images from the left heart catheterization in a Heartmate II (b) and HeartWare (c) patient. Blue arrows represent location of the aortic guide catheter. Red arrows represent location within the LV of the high-fidelity pressure wire distant from the inflow cannula.

Supplemental Video Legends

Video S1. Representative setup for combined LHC/RHC in a patient supported with a HeartMate II LVAD. A high-fidelity pressure wire is shown in the left ventricle, posterior to the inflow cannula with a 5-Fr. multipurpose guide catheter in the ascending aorta and balloon-tipped catheter in the right ventricle. Best viewed with Windows Media Player.

Video S2. Representative setup for combined LHC/RHC in a patient supported with a HeartWare LVAD. A high-fidelity pressure wire is shown in the left ventricle inferior to the inflow cannula with 5-Fr. multipurpose guide catheter in the ascending aorta and balloon-tipped catheter in the pulmonary artery. Best viewed with Windows Media Player.