Circulation: Heart Failure

ORIGINAL ARTICLE

Impact of Hemodynamic Ramp Test-Guided HVAD Speed and Medication Adjustments on Clinical Outcomes

The RAMP-IT-UP Multicenter Study

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BACKGROUND: Hemodynamic ramp (HR) tests can guide the optimization of left ventricular assist device (LVAD) speed and direct medical therapy. We investigated the effects of HR-guided LVAD management.

METHODS AND RESULTS: This prospective, multicenter, randomized, pilot study compared outcomes in LVAD patients using an HR-guided (HR group) versus a standard transthoracic echocardiography-guided (control group) management strategy. Patients were enrolled and randomized 1 to 3 months post-HVAD implantation and followed for 6 months. Twenty-two patients (57±10 years, 73% male) were randomized to the HR group and 19 patients (51±13 years, 63% male) to the control group. HR group patients had double the number of LVAD speed changes (1.68 versus 0.84 changes/patient, P=0.09 with an incidence rate ratio 2.0, 95% CI, 0.9–4.7) with twice the magnitude of rotations per minute changes (130 versus 60 rotations per minute/patient, P=0.004) during the study. The HR group also had 2-fold greater heart failure medication changes (4.32 versus 2.53 changes/patient, P=0.072, incidence rate ratio 1.7 with 95% CI, 0.8–3.5) predominantly because of changes in diuretic dose (40 versus 0 mg/patient, P<0.001). The HR group had numerically but not statistically higher event-free survival (62% versus 46%, P=0.087; hazard ratio, 0.46 with 95% CI, 0.2–1.2), with numerically but not statistically lower events per patient-year (P=0.084). There were no significant differences in the 6-minute walk or Kansas City Cardiomyopathy Questionnaire tests at 6 months.

CONCLUSIONS: In this randomized pilot study of LVAD patient management we demonstrated the feasibility of standardized HR testing at multiple institutions and that a strategy guided by hemodynamics was associated with more LVAD speed and medication adjustments and a nonsignificant reduction in adverse events. A pivotal study to demonstrate the clinical benefit of HR testing is warranted.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT03021239.

Key Words: echocardiography ■ heart failure ■ hemodynamics ■ mortality ■ survival

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WHAT IS NEW?

- RAMP-IT-UP is a prospective, multicenter, randomized trial demonstrating for the first time that a strategy using hemodynamic ramp testing had an advantage over a conventional standard-of-care approach resulting in better clinical outcomes with more device speed and medication adjustments in patients with HVAD left ventricular assist devices.

WHAT ARE THE CLINICAL IMPLICATIONS?

- A pivotal study to demonstrate the clinical benefits of hemodynamic ramp testing is warranted to define the optimal patient management strategy during left ventricular assist device therapy.

Continuous-flow left ventricular assist devices (LVAD) have improved survival rates of selected patients with Stage D heart failure (HF) and are widely used both as a bridge to transplantation and as destination therapy.[1–4] However, LVAD patients experience high rehospitalization rates because of multiple complications, including HF and hemocompatibility-related adverse events (HRAEs).[5] As a result, recent efforts in the LVAD field have shifted focus towards the identification of strategies that can reduce adverse events and improve quality of life.

Successful LVAD therapy depends on continued active management following implantation. Although the LVAD can successfully treat HF symptoms, this is predicated on the fact that pump speed is optimized and that concomitant medical therapy is properly used. Traditionally echocardiography has been used to adjust LVAD speed to achieve proper unloading. However, recent studies suggest that measurement of hemodynamics can provide crucial additional information for clinicians to better optimize LVAD function and hence patients' symptoms. Hemodynamic ramp (HR) testing is effective in guiding patient management to achieve more normal hemodynamic profiles, even in apparently stable well-compensated LVAD patients,[6] and furthermore, such hemodynamics-guided management has been associated with a reduction in adverse events.[7,8] However, a hemodynamic management strategy is more invasive than echocardiographic managements and has not been evaluated in a prospective randomized study and its use had, therefore, been limited.

RAMP-IT-UP was a prospective multicenter randomized pilot study designed to assess the feasibility of implementing a standardized HR testing protocol across multiple centers, to determine the impact on pump and medical management, and to assess the impact on adverse events and quality of life. We also aimed to assess the potential magnitude of effect of the HR test-based patient management strategy on clinical outcomes to inform the design of a fully powered pivotal randomized study.

METHODS

Trial Objective and Organization

The prospective, multicenter, randomized, unblinded RAMP-IT-UP pilot study compared rates of adverse events in patients whose LVAD speed and medical therapies were guided by HR tests versus those in patients who were managed according to current standard-of-care guidelines, which are based on clinical assessment and transthoracic echocardiography (TTE).[9] The trial was conducted at 4 sites in the United States and was supervised by a Data Coordinating Center (University of Chicago). Data were collected on electronic case report forms that were completed by study coordinators at each site. In addition to providing oversight of individual trial sites, the Data Coordinating Center compiled all study data and conducted all statistical analyses. The authors had unrestricted access to the data and attested to the completeness and accuracy of the data. The trial was approved by the institutional review board at each site. The study was funded by a grant from Medtronic (Minneapolis, MN). The sponsor did not have access to trial data and did not participate in data analysis or the writing of the article.

Patient Selection

Patients 18 years of age or older, who were discharged from the hospital after a first-time Heartware ventricular assist device (HVAD) (Medtronic, Minneapolis) implant and were 1 to 3 months postimplantation were eligible for enrollment. Patients who had undergone an invasive hemodynamic assessment after removal of the perioperative pulmonary artery catheter were excluded. A complete list of inclusion and exclusion criteria are provided in the Appendix in the Data Supplement. All participants provided written informed consent.

Trial Procedures

Study participants were randomly assigned, in a 1:1 ratio, to either a hemodynamic-guided management strategy using an HR test (HR group) or a standard clinical and TTE-guided management strategy (control group).[9] Randomization was performed in blocks of 4 by site. After enrollment, baseline demographic characteristics, medical history, medications, laboratory data, device parameters, TTE data, and preoperative hemodynamic data were obtained. Additional baseline testing included 6-minute walk distance and the Kansas City Cardiomyopathy Questionnaire (KCCQ).

After randomization, patients in the HR group underwent an HR test. The complete HR protocol is detailed in the Appendix in the Data Supplement. Briefly, after confirming adequate anticoagulation, right heart catheterization was performed. A complete set of hemodynamic data (central venous pressure, pulmonary artery pressures, pulmonary capillary wedge pressure [PCWP], mixed venous oxygen saturation, thermodilution cardiac index, and blood pressure) and echocardiographic measurements were recorded at the patient's initial baseline HVAD speed. The HVAD speed was then lowered

to 2300 rotations per minute (RPM) with repeat collection of hemodynamic and echocardiographic data. The HVAD speed was then increased in 100 RPM increments to a maximum of 3200 RPM with repeat data collection at each interval.

LVAD speed was adjusted at the end of the HR study based on the hemodynamic and echocardiographic findings. Speed could be increased, decreased, or left the same with the primary goal of hemodynamic optimization according to the following criteria: central venous pressure <12 mm Hg, PCWP <18 mm Hg, and cardiac index >2.2 L/min per m^2. Echocardiographic parameters, such as intermittent aortic valve opening, minimal or no mitral regurgitation, minimal or no aortic regurgitation, and LV size, could be used as secondary objectives when setting speed. In addition, the detection of suction, either echocardiographically or based on the HVAD waveform, could inform final speed choice. In situations with very low PCWP (<8 mm Hg), speed could be decreased to prevent suction events. In the event that the hemodynamic goals could not be achieved by RPM adjustments alone, adjustments were made to medical therapies (diuretics and neurohormonal blockade) following the HR study.

Patients in the control group were managed based on clinical assessments and TTE findings according to International Society for Heart and Lung Transplantation guidelines, which recommend unloading the LV while maintaining a midline interventricular septum and minimizing mitral regurgitation, with a secondary goal of allowing intermittent aortic valve opening.[9] In addition, medications were adjusted to manage volume status and blood pressure based on clinical assessments.

Patients in both groups were seen at 1 week, 1 month, 3 months, and 6 months after randomization (Figure 1). Data collected at each visit included clinical status, device parameters, medications, 6-minute walk test, KCCQ, and adverse events.

Study End Points

Because this was designed as a pilot study, it was not powered to provide statistically significant results for any one parameter. Instead, the goal of this study was to determine if patient management was influenced by the results of the ramp test and to identify clinical parameters most likely to be impacted by this management strategy. This information is critical for determining the appropriate sample size for a fully powered study. The prospectively defined end points included

1. Survival free from any device-related complications.
2. Device-related complications: HF readmissions, stroke, pump thrombosis, gastrointestinal bleeding, arrhythmias, and driveline infections. Complications were defined according to definitions provided by the Interagency Registry for Mechanically Assisted Circulatory Support.[10]
3. Change in 6-minute walk test.
4. Change in KCCQ score.

In addition, we assessed HRAEs which were defined as LVAD-related bleeding or thrombotic abnormalities as described previously.[5] These events were further classified into nonsurgical bleeding (gastrointestinal or other nonsurgical bleeding episodes >30 days posttransplant), neurological events (stroke or other neurological events), and thromboembolic events (pump thrombosis and arterial thromboembolism). A tiered hierarchal score (hemocompatibility score) was calculated for each patient by weighing each event considering its escalating clinical relevance, to determine the aggregate net burden of HRAEs (Table I in the Data Supplement).

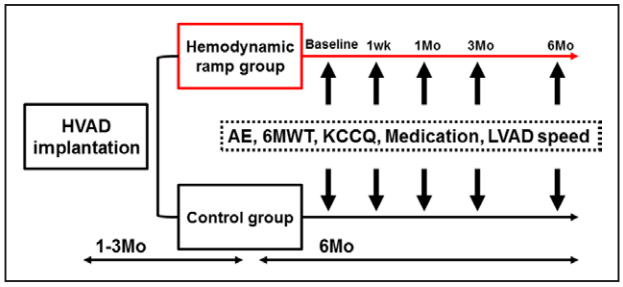

Figure 1. Study protocol.
6MWT indicates 6-minute walk test; AE, adverse event; KCCQ, Kansas City Cardiomyopathy Questionnaire; and LVAD, left ventricular assist device.

Statistical Analyses

Clinical data obtained from each site were entered into a REDCap database. Statistical analyses were performed with SPSS Statistics 22 (SPSS Inc, Armonk, IL). Two-sided *P* values <0.05 were considered statistically significant. Continuous data were presented as means and SDs or median and interquartile for continuous data considering their distribution. Categorical data were expressed as frequency with percentages. Event rates were expressed as events per patient-year. Continuous variables were compared between the 2 groups with an unpaired *t* test or the Mann-Whitney *U* test depending on their distribution. Several variables such as event rates were expressed as average for better understanding, irrespective of their distribution normality. Categorical variables were compared between the 2 groups using the Fisher exact test. Numbers of times of treatment changes were compared between the 2 groups using negative binomial regression analyses. Event-free survival was assessed by Kaplan-Meier survival analyses and compared between the 2 groups by the log-rank test and Cox proportional hazard ratio regression analysis.

RESULTS

Baseline Characteristics

In total, 41 patients with HVAD were enrolled from 4 experienced academic medical centers in the United States (16 at University of Chicago; 11 at Northwestern University; 5 at Stanford University; and 11 at University of Utah). Patients were randomized at a median of 1.7 months following LVAD implantation (interquartile range, 1.3–2.2 months). Twenty-two patients were randomized to the HR group and 19 to the control group. The HR patients were numerically older and more likely to be white (Table 1). Laboratory and preimplant hemodynamic data were not significantly different between the 2 groups. However, the patients in the HR group had a greater degree of preimplant

Table 1. Pre-HVAD Baseline Characteristics

	HR (N=22)	Control (N=19)	*P* Value
Demographic data			
Age, y	56.5±10.3	50.7±13.2	0.13
Male sex	16 (73%)	12 (63%)	0.74
Race			
White	16 (73%)	6 (32%)	0.01*
Black	3 (14%)	7 (37%)	0.084
Other	3 (14%)	6 (32%)	0.17
Body mass index	25.4±4.6	28.0±8.0	0.21
Destination therapy	9 (41%)	12 (63%)	0.22
Ischemic cause	6 (27%)	9 (47%)	0.16
Hypertension	9 (41%)	6 (32%)	0.75
Diabetes mellitus	4 (18%)	7 (37%)	0.29
History of stroke	2 (9%)	0 (0%)	0.18
Atrial fibrillation	9 (41%)	9 (47%)	0.76
History of VT	6 (27%)	7 (37%)	0.79
Chronic obstructive pulmonary disease	3 (14%)	2 (11%)	0.28
Obstructive sleep apnea	2 (9%)	6 (32%)	0.09
Laboratory data			
Hemoglobin, g/dL	11.4±1.8	11.8±2.3	0.46
Serum sodium, mEq/L	136±5	134±10	0.42
Serum creatinine, mg/dL	1.4±0.9	1.3±0.7	0.77
Plasma NT-proBNP, pg/mL	2896 (667, 7650)	1697 (398, 7175)	0.90
Preoperative hemodynamic data			
CVP, mm Hg	11±6	14±7	0.22
PCWP, mm Hg	26±8	25±9	0.73
CI, L/min per m^2	1.94±0.39	1.95±0.50	0.95
CVP <12 mm Hg	8/13 (62%)	5/11 (45%)	0.35
PCWP <18 mm Hg	5/18 (28%)	5/16 (31%)	0.82
CI >2.2 L/min per m^2	4/18 (22%)	4/17 (24%)	0.93
PVR, WU	3.2 (1.5, 4.1)	2.4 (1.6, 4.0)	0.91
PAPi	2.5 (1.7, 5.6)	1.7 (1.0, 3.6)	0.19
Preoperative echocardiographic data			
LVDd, cm	6.8±1.3	6.3±0.8	0.16
LVEF, %	18±5	21±11	0.27
MR, grade	3 (2, 4)	2 (2, 4)	0.026*
TR, grade	2 (1, 3)	2 (1, 4)	0.43

Continuous variables were compared between 2 groups using the unpaired *t* test or Mann-Whitney *U* test as appropriate. Categorical variables were compared between 2 groups using the Fisher exact test. BNP indicates B-type natriuretic peptide; CI, cardiac index; CVP, central venous pressure; HR, hemodynamic ramp; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; TR, tricuspid valve regurgitation; and VT, ventricular tachyarrhythmia.

*$P<0.05$.

mitral regurgitation. On discharge from the index hospitalization, there were no statistically significant differences between the 2 groups (Table 2).

Table 2. Clinical Variables at Discharge From the Index HVAD Implantation Hospitalization

	HR (N=22)	Control (N=19)	*P* Value
LVAD speed, RPM	2700±136	2620±124	0.054
Medications			
β–blocker	7 (32%)	9 (47%)	0.96
ACE inhibitor	16 (73%)	11 (58%)	0.41
Aldosterone antagonist	8 (36%)	9 (47%)	0.17
Laboratory data			
Hemoglobin, g/dL	9.2±0.9	9.0±1.6	0.64
Serum creatinine, mg/dL	1.0±0.7	1.0±0.4	0.98
Plasma NT-proBNP, pg/mL	861 (568, 6124)	1491 (547, 2768)	0.52
Echocardiographic data			
LVDd, cm	6.2±1.5	5.3±1.1	0.051
LVEF, %	21±5	26±14	0.13
MR, grade	1 (0, 2)	1 (0, 1)	0.18
TR, grade	2 (1, 4)	2 (1, 4)	0.85

Continuous variables were compared between 2 groups using the unpaired *t* test or Mann-Whitney *U* test as appropriate. Categorical variables were compared between 2 groups using the Fisher exact test. ACE indicates angiotensin-converting enzyme; BNP, B-type natriuretic peptide; HR, hemodynamic ramp; LVAD, left ventricular assist device; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; and TR, tricuspid valve regurgitation.

HVAD Speed Management in the HR Group

Among the 22 patients who were assigned to the HR arm, 1 patient declined HR testing, and thus 21 patients underwent the procedure. No adverse events were reported during these procedures. Overall, 7 patients had their speed increased, and 8 patients had their speed decreased at the end of the HR study. Comparison of hemodynamic profiles before and after the ramp test (ie, at the baseline HVAD speed and at the post-ramp final set HVAD speed) are summarized in Table 3. Among 14 patients who already had optimized hemodynamics at baseline LVAD speed, LVAD speed was decreased in 6 patients to achieve intermittent aortic valve opening and increased in 2 patients because their hemodynamics were on the borderline of the set criteria and could be further improved on. At the completion of the study, 14/21 (67%) patients achieved hemodynamic optimization (as described in the Methods section) at the set LVAD speed.

HVAD Speed Management in the Control Group

For the patients in the control group, LVAD speed was set at the discretion of the treating physician as described in Methods. LVAD speed was increased in 5 patients and decreased in 1 patient at the baseline

Table 3. Hemodynamic Data During Ramp Tests in the Hemodynamic Ramp Group

	Baseline LVAD Speed	Set LVAD Speed	Change
LVAD speed, RPM	2683±144	2715±124	0 (–20, 30)
LVDd, cm	5.6±1.3	5.9±1.2	0 (–0.1, 0.3)
Heart rate, bpm	84±13	86±13	0 (–2, 0)
Mean arterial pressure, mm Hg	88±13	86±14	0 (–4, 5)
CVP, mm Hg	7.4±4.8	6.9±4.3	0 (0, 1)
PCWP, mm Hg	12.4±5.3	13.0±5.3	0 (0, 1)
CI, L/min per m^2	2.56±0.43	2.56±0.45	0 (–0.10, 0.10)
CVP <12 mm Hg	17 (81%)	18 (86%)	…
PCWP <18 mm Hg	18 (86%)	17 (81%)	…
CI >2.2 L/min per m^2	17 (81%)	17 (81%)	…
Hemodynamic optimization	14 (67%)	14 (67%)	…

Data presented as mean±SD, n (%), or median (IQR). CI indicates cardiac index; CVP, central venous pressure; IQR, interquartile range; LVAD, left ventricular assist device; LVDd, left ventricular diastolic diameter; PCWP, pulmonary capillary wedge pressure; and PVR, pulmonary vascular resistance.

visit. Overall, mitral regurgitation grade decreased from 2.5±1.2 to 0.9±0.8, with a reduction in LV diameter from 6.3±0.8 to 5.3±1.1 cm (Table 2). Among the 19 patients assigned to the control group, 3 underwent right heart catheterization at the discretion of the primary physician, each during a hospital readmission for HF; these occurred 3 or more months following randomization.

HVAD Speed Adjustment During the Observation Period

Changes of LVAD speed during the observation period are shown in Figure 2A for both groups. LVAD speeds were more frequently adjusted in the HR group than the control group, even at later points in the study remote from the conduct of the ramp test. The maximum LVAD speed change in the HR group was 300 RPM, whereas the maximum LVAD speed change was 160 RPM in the control group. The number of LVAD speed changes averaged 1.68 per patient in the HR group versus 0.84 per patient in the control group (*P*=0.09; Figure 2B). The average absolute change of HVAD speed was significantly higher in the HR group compared with the control group (130 [100, 280] versus 60 [0, 100] RPM per patient, *P*=0.004; Figure 2C).

Among the 7 patients in the HR group with a speed increase at the time of the HR study, only one had their speed decreased at the 1-week follow-up visit. One other patient in this group finished the study with a speed below the speed set at the end of the HR study (speed initially increased by 40 RPM and then decreased by 60 RPM at the 3-month visit). Among the 5 patients in the control group with a speed increase at the baseline visit, 1 had speed decreased by 60 RPM at 1 month at the time of driveline infection, and the other 4 patients' speed remained unchanged for the rest of the study.

Medication Adjustment During the Observational Period

Trends of medication doses during the observational period are summarized in Figure 3. β-blocker doses were changed more frequently in the HR group (*P*=0.084; Figure 3A), and the absolute dose change was higher in the HR group (6.9 mg/d [0, 37.3 mg/d] versus 6.3 mg/d [0, 12.5mg/d], *P*=0.007; Figure 3B). Likewise, diuretic doses were changed more frequently in the HR group (*P*=0.069; Figure 3A), and the absolute dose change was higher in the HR group (40 mg/d [0, 105 mg/d] versus 0 mg/d [0, 40 mg/d], *P*<0.001; Figure 3B). Changes in angiotensin-converting enzyme inhibitors doses were similar in both groups (*P*>0.05; Figure 3A and 3B). As a result, changes in all 3 medications in the HR group were more frequent than in the control group though this difference was not statistically significant (4.32 versus 2.53 changes/patient, *P*=0.07, incidence rate ratio 1.7 with 95% CI, 0.8–3.5).

Adverse Events

During the 6-month observation period, 7 events were observed in 7 (33%) patients in the HR group and 13 events in 9 (47%) patients in the control group. There were no patient deaths in either group during the study period.

Because of the small number of patients enrolled in this pilot study, there were no statistically significant differences in event rates between HR and control groups. HF readmission rate was 0.46 events/patient-year in the HR group compared with 0.64 events/patient-year of control group (*P*=0.63; Figure 4A). The rate of any device-related event was 0.65 events/patient-year in the HR group compared with 1.39 events/patient-year in the control group (*P*=0.084; Figure 4B). By Kaplan-Meier analysis through 6 months of follow-up, event-free survival was 62% in the HR group compared with 46% in the control group yielding a hazard ratio of 0.46 and 95% CI, 0.17 to 1.24 (*P*=0.089; Figure 4C).

The HR group also had a lower hemocompatibility score with fewer Tier I and Tier IIIB HRAEs that did not reach statistical significance (0.05 versus 0.37 score, *P*=0.11; Figure 4D).

Quality of Life Assessment and Exercise Tolerance

KCCQ scores were not significantly different at baseline between the 2 groups (*P*=0.22). KCCQ scores

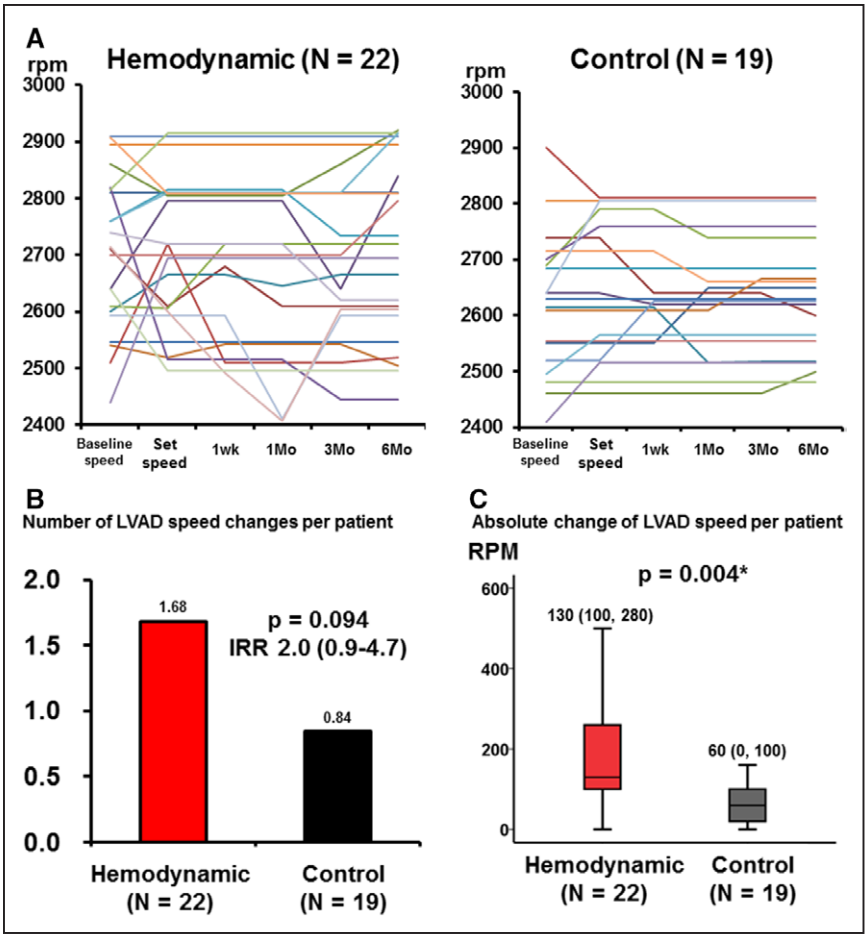

Figure 2. Trends of the absolute value of left ventricular assist device (LVAD) speed (A), number of LVAD speed changes per patient (B), and absolute change of LVAD speed per patient (C) between the hemodynamic ramp (HR) arm and the control arm.
IRR indicates incidence rate ratio.

rose in both groups during the study period, with no statistically significant difference between groups at any of the study time points (Figure 5A). Similarly, 6-minute walk distance increased in both groups throughout the study, with no statistically significant difference between groups at any study time points (Figure 5B). There were no statistically significant differences in the mean blood pressures between the 2 groups during the study period (P>0.05 for all; Table II in the Data Supplement).

DISCUSSION

In this prospective, multicenter, randomized, nonblinded pilot study, we evaluated the impact of a patient management strategy guided by HR tests on outcomes fol-

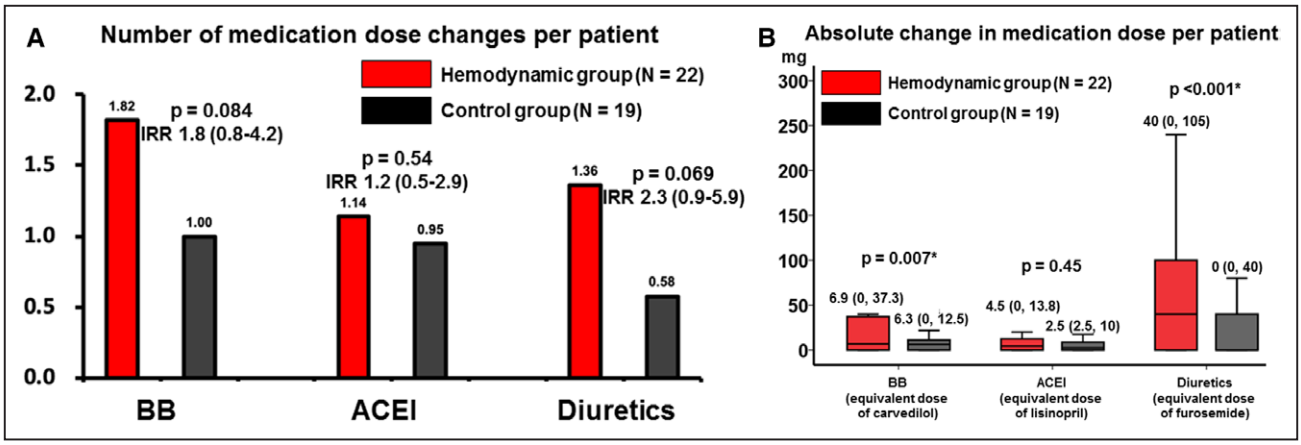

Figure 3. Number of dose changes per patient for β-blockers (BB), ACE (angiotensin-converting enzyme) inhibitors, and diuretics during the course of the study (A) and absolute changes in the doses of BB, ACE inhibitor, and diuretics during the course of the study (B).
Numbers of dose changes per patient were compared by negative binomial regression analyses. Absolute changes were compared by Mann-Whitney U test. IRR indicates incidence rate ratio. *P<0.05.

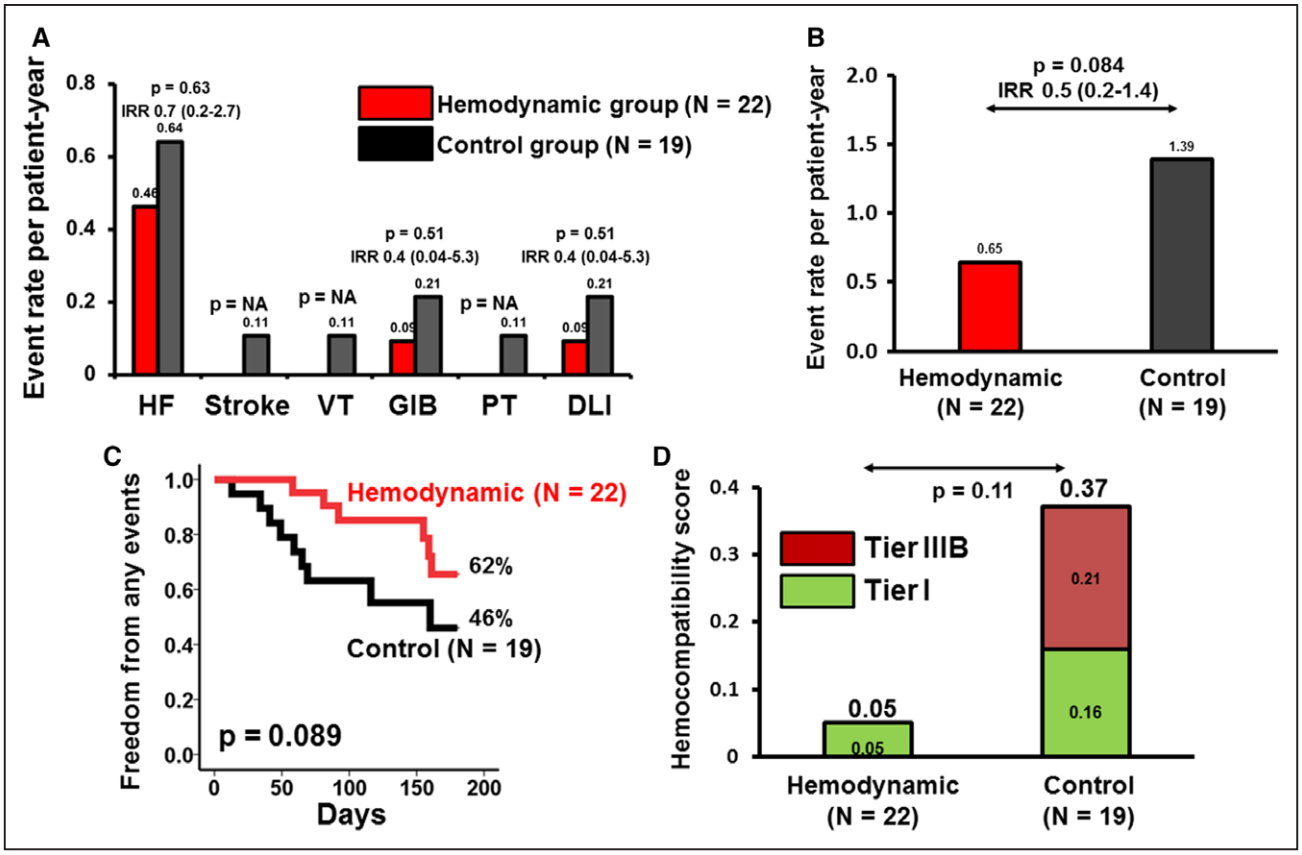

Figure 4. Rates of individual adverse events (A) and total event rates (B) in the hemodynamic ramp (HR) arm and the control arm.
C, Kaplan-Meier survival analysis of freedom from any adverse events. **D**, Comparison of hemocompatibility score between the HR arm and the control arm. Event rates were compared by negative binomial regression analyses. Hemocompatibility scores were compared using the Mann-Whitney *U* test. Kaplan-Meier curves were compared by log-rank test. DLI indicates driveline infection; GIB, gastrointestinal bleeding; HF, heart failure; IRR, incidence rate ratio; PT, pump thrombosis; and VT, ventricular tachyarrhythmia. **P*<0.05.

lowing LVAD implantation. There are 3 primary findings. First, we demonstrated the feasibility of performing protocolized HR studies at multiple LVAD programs; this is important because such ramp studies were not previously routine practice at 3 of the 4 centers involved in the study. Second, despite the small sample size, it was demonstrated that the availability of hemodynamics in the HR group was associated with a significantly greater number of LVAD speed changes and HF medication dose adjustments during the study period. Third, analysis of clinical outcomes showed numerically lower rates of adverse events in the HR group, which were most apparent for HF and overall hemocompatibility-related events, though these differences were not statistically significant. Accordingly, this study provides preliminary support for the hypothesis that adjustments of LVAD speed

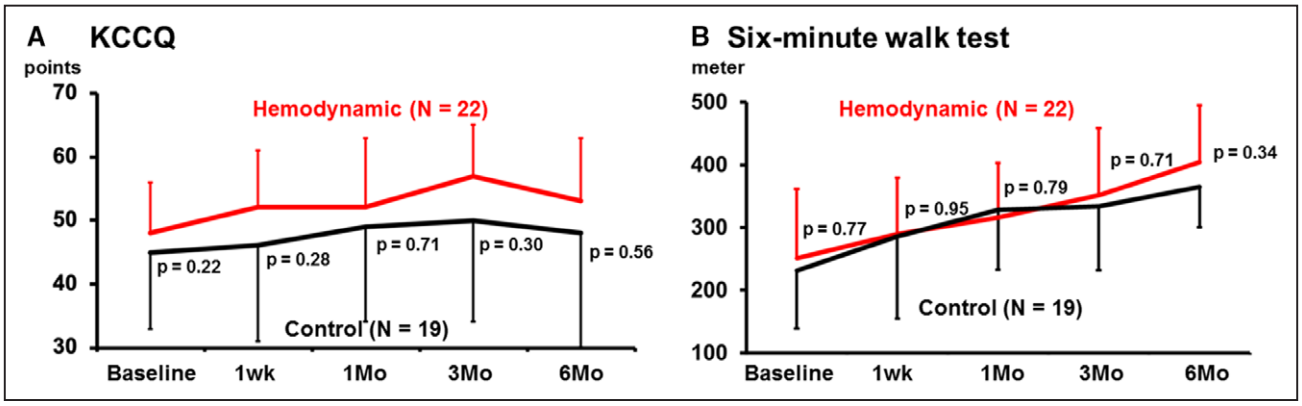

Figure 5. Comparison of Kansas City Cardiomyopathy Questionnaire (KCCQ) score (A) and 6-minute walk distance (B) between the hemodynamic ramp (HR) arm and the control arm over the course of the study.
Variables at each time point were compared between the 2 groups using the unpaired *t* test.

and medical therapies based on the results of HR tests may have a meaningful impact on clinical outcomes and provides sufficient data to estimate the sample size for a fully powered study to test this hypothesis.

It is now well established that LVADs significantly improve longevity and quality of life in patients with advanced HF. In 2017, >3000 patients were implanted with a durable LVAD, and it is anticipated that this number will grow over the next several years. However, only a small percentage of potentially eligible advanced HF patients ever receive an LVAD. This is believed to be largely because of the high rate of complications and readmissions which limit acceptance of this form of therapy among patients and referring physicians. Indeed, in the most recent LVAD study, the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate3, there were 2.1 hospitalizations per patient-year, with a 10% incidence of stroke, 27% incidence of gastrointestinal bleeding, 24% incidence of ventricular arrhythmias, and 24% incidence of driveline infections.[1,2,11]

To date, LVAD randomized clinical trials have primarily evaluated comparative device effectiveness. While there have been previous studies that randomized different management strategies in LVAD patients, they have been short-term physiological studies and have not used clinical events as an outcome.[12] Hereby, we present the first study with intermediate-term follow-up to randomize LVAD patients to 2 different management strategies and follow clinical outcomes. The first achievement of the current study is the demonstration of the feasibility of implementing different LVAD treatment protocols in a randomized fashion at 4 large medical centers.

As noted, the results of this study provide prospective, preliminary support that the use of a hemodynamic strategy for long-term management of LVAD patients may improve outcomes. The 2013 International Society for Heart and Lung Transplantation guidelines advocated use of an echocardiographic approach to setting LVAD speed, recommending achievement of a midline septal position, minimization of mitral regurgitation and intermittent aortic valve opening.[9] However, Uriel et al. emphasized the importance of also assessing LV unloading at different speeds and highlighted the fact that the relationship between echocardiographic parameters and changes in LVAD speed varied among different pumps.[13–15] For the axial-flow HeartMate II, this relationship remains linear throughout the range of LVAD speeds, while in centrifugal-flow pumps (HVAD and HeartMate 3), the relationship is non-linear with an increased rate of LV decompression following closure of the aortic valve. More importantly, several groups demonstrated the additional benefits of adding hemodynamic measurements to the echocardiographic data obtained during the ramp study.[6,16,17] Our group showed that LV unloading based on echocardiography as currently utilized is a poor surrogate for hemodynamic unloading, with nearly 50% of clinically stable LVAD outpatients having marked elevations of central venous pressure and/or PCWP or suboptimal cardiac outputs at optimal echocardiographic settings.[6] These findings prompted the question of whether optimization of patients' hemodynamics through LVAD speed and medical therapy adjustments can improve outcomes. Subsequently, Imamura et al[7] demonstrated that LVAD patients in whom optimal hemodynamics had been achieved exhibited a significantly higher rate of survival free of HF. Furthermore, the same group reported that hemodynamic optimization was associated with a lower rate of HRAEs (ie, strokes, gastrointestinal bleeding and pump thrombosis).[8] However, both of these studies were based on nonrandomized and single-center experiences raising the possibility that hemodynamic optimization is merely a marker of a healthier patient rather than being mechanistically linked to reduced adverse events. The current study was designed to further address this question in a randomized fashion, to provide a proof-of-concept and to inform design of an adequately powered study to assess the clinical benefits of an HR test-guided LVAD management strategy.

In contrast to adverse events, no appreciable impact of hemodynamic-based management was detected on HF-specific measures of quality of life or in an assessment of exercise tolerance (6-minute walk). It could be that longer periods of time post-LVAD implantation are required to fully evaluate the impact of hemodynamic optimization on these parameters.

The role of hemodynamic measurements in the management of HF patients has been a topic of great debate over the past 15 years. The role of hemodynamic-guided medical therapy was investigated in the ESCAPE trial (Evaluation Study of Congestive HF and Pulmonary Artery Catheterization Effectiveness), in which pulmonary artery catheter monitoring did not improve short-term outcomes in (non-LVAD) HF patients with acute decompensated HF.[18] The study led to a significant reduction in the use of pulmonary artery catheters in HF patients, even in those that might not have been included in ESCAPE.[19] However, a post hoc analysis of the ESCAPE trial found that persistently elevated filling pressures at the end of the trial were strong predictors of worse postdischarge outcomes, emphasizing the importance of hemodynamic optimization in HF.[20] More recently, in the CHAMPION trial (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III HF Patients), use of an implanted pulmonary artery sensor led to a 30% reduction in HF readmissions in non-LVAD patients.[21,22] This outcome was attributed to a higher rate of changes to diuretic therapy and neurohormonal blockade in the group with active hemodynamic monitoring.[23] The present study further supports the potential benefits of hemodynamic monitoring in the LVAD-supported subset of HF patients. Although underpowered

to detect statistically significant differences in event rates between groups, it is notable that the HR group had consistently fewer events than the control group across all types of adverse events. Mirroring the CHAMPION Study, patients in the HR group in our study had significantly more alterations in medical therapy, in addition to speed adjustments, during the study. In addition, there were a significantly greater number of medication dose changes in the HR group, particularly in diuretics. As with the CHAMPION study, the availability of hemodynamic data resulted in more active management with numerically fewer, but not significantly reduced, adverse events.

Hemodynamic measurements performed at a single point in time and continuous pulmonary pressure monitoring represent different forms of patient management. However, the present study suggests that even a hemodynamic snapshot in time is better than clinical assessments alone as it relates to patient management and perhaps leaves the provider feeling comfortable making subsequent changes in device speed more often with significantly larger changes once hemodynamics are known. Furthermore, providers may feel more comfortable changing medications with this information. This study emphasizes the need to evaluate the role of continuous hemodynamic assessments in LVAD patients.

Regarding potential mechanisms, reduced adverse events in an HR group may be secondary to HVAD speed optimization, intensification of medical therapy, or a combination of both. First, at the simplest level, knowledge of central venous pressure and PCWP provides strong evidence of overall volume status which, as noted above, we have shown to be inaccurately assessed by standard clinical examination in LVAD patients.[13–15] Indeed, diuretic adjustments accounted for the single most frequent adjustment to medical therapy in our study. Second, it is notable that HVAD speed was more frequently adjusted during the entire follow-up period and not just at the time of the ramp test. This suggests that clinicians were more aware and subsequently more attentive to the management of patients who failed to achieve hemodynamic optimization at the time of the test. This is an obvious advantage of HR test over the hemodynamic assessment at a single LVAD speed. Repeat ramp tests may provide even more guidance to adjust LVAD speed and medications during long-term LVAD support, but the potential benefits would have to be weighed against the invasiveness of the test. Third, HF is associated with significant increases in inflammatory markers (eg, TNF-α [tumor necrosis factor alpha]) and markers of angiogenesis (eg, angiopoietin-2) that are associated with increased risk of adverse events, such as arteriovenous malformations and strokes.[24–26] Optimizing hemodynamics may reduce inflammation and reduce those risks. Finally, while the role of neurohormonal blockade in LVAD patients is not proven, more aggressive use of HF medications may also improve the HF milieu (including intrinsic right ventricular and LV function) that can contribute to improved outcome. These questions will be the main focus of a larger, randomized study.

Limitations

The results of the present study need to be interpreted within the context of several limitations. First, this is a pilot study with a small sample size that was not powered to detect differences in outcomes. Accordingly, the results from this study are hypothesis-generating and provide crucial data to inform the design of a pivotal study. Second, because of the small sample size, some differences in baseline characteristics were noted. In particular, the patients in the HR arm were older with more dilated left ventricles and higher BNP (B-type natriuretic peptide) levels. Third, the study only included patients supported by an HVAD LVAD; outcomes and management strategies as they relate to both hemodynamics and hemocompatibility events may differ among devices. Finally, the study was unblinded. Lack of influence of a placebo effect on the patients is supported by the lack of improvements in quality of life measures and 6-minute hall walk distance. However, knowledge of patient assignment could have impacted physician and LVAD coordinator behavior in the care of these patients. Because the invasive nature of hemodynamic measurements may ultimately preclude blinding, this potential effect will need to be factored into the design of future pivotal studies.

Conclusions

Based on the results of the RAMP-IT-UP pilot study, the HR test provides a safe and feasible strategy for the optimization of LVAD speed and medical therapies. Use of the HR tests was associated with significantly greater numbers of LVAD speed and medication adjustments. A large, randomized pivotal study of HR-guided LVAD patient management is warranted.

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