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Heart Failure (W Tang, Section Editor)

How to Optimize Patient Selection and Device Performance of the Newest Generation Left Ventricular Assist Devices

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Abstract

Purpose of review This review will discuss key differences of third-generation left ventricular assist devices (LVADs), identify patient selection considerations to optimize post-implant clinical outcomes, and summarize key echocardiographic and hemodynamic parameters to guide device optimization.
Recent findings There are major engineering differences between the third-generation LVADs which contribute to unique pump operational characteristics. Improved hemocompatibility has led to reduction in hemocompatibility-related adverse events (HRAEs), particularly for the Heartmate 3 pump. Having an optimal hemodynamic profile compared with not while on LVAD support defined by either echocardiography or right heart catheterization is associated with a more favorable event-free survival.
Summary With attentive patient selection, use of current third-generation LVADs, and appropriate use of echocardiography and invasive ramp studies, LVAD therapy will continue to improve survival and quality of life in select patients with advanced heart failure.

Introduction

Tremendous strides have been made in the field of mechanical circulatory support (MCS) in recent years. The first-generation left ventricular assist devices (LVADs) were pulsatile devices, such as the Heartmate XVE, and were mechanically limited by device durability. Second-generation LVADs include the continuous flow (CF) axial flow devices, such as the Heartmate II. Advancements in LVAD engineering have led to smaller and more hemocompatible devices. Third-generation LVADs are centrifugal devices consisting of the HeartWare (HVAD) by Medtronic and Heartmate 3 (HM3) by Abbott. With FDA approval of HM3 for bridge to transplant (BTT) indication in 2017 followed by approval for destination therapy (DT) indication in 2018, HM3 has largely replaced the older generation HMII. Therefore, the main focus of this article will be on the centrifugal flow HVAD and HM3 devices with a primary aim to review patient selection and device-related characteristics and define device optimization strategies to enhance post-LVAD clinical outcomes.

Patient selection

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) has devised a standard scale to classify patients by heart failure severity, ranging from 1 to 7, with one being the sickest patients [1••]. Based on INTERMACS, LVADs have been used in the sickest patients with advanced heart failure—INTERMACS (IM) profiles 1–3. However, peri-operative mortality is the highest in INTMERACS profile 1 patients [2•]. The ROADMAP study showed survival with improved functional status and was better in selecting patients with HMII LVAD compared with optimal medical management (OMM) in ambulatory, non-inotrope-dependent IM profiles 4 to 7 patients [3••]. For IM profile 4, more LVAD patients met the primary endpoint compared with OMM patients (40% versus 15%; odds ratio = 3.9 [1.2 to 12.7], $p = 0.024$), but there was no statistically significant difference for IM 5 to 7. In addition, composite endpoints of survival on original therapy with improved health-related quality of life or depression were better with LVAD than OMM in IM4, but not IM 5–7 even with adverse events generally being more frequent in those supported by the HMII compared with OMM in this study [4•].

Despite these established observations, only a minority of LVADs are being placed in ambulatory patients with advanced heart failure. Based on the ENDURANCE Supplemental trial that compared patient outcomes related to the HVAD and HMII device, the majority of patients were IM profile 3 (43%) and profile 2 (33%) patients, with a smaller representation from INTERMCAS profiles 4–7 (20%) and profile 1 (3–4%) [5•]. Similarly, the MOMENTUM 3 full cohort report, comparing HM3 with HMII devices enrolled mostly INTERMACS profile 3 (approximately 50%) and 2 profiles (30%) with only approximately 15% deemed profile 4 and 2–3% deemed profile 1 [6••].

There are several recognized relative contraindications to LVAD therapies. In a cohort of patients undergoing HMII and HVAD implants, multivariate logistic regression analysis identified high pre-operative central venous pressure and older age as independent predictors of 90-day post-operative mortality [7•].

The severity of end organ damage also predicts poor outcome after LVAD implant [8•]. A number of risk models have been validated to predict mortality after LVAD implant. The HMII risk score has been validated in both HMII and HVAD continuous flow LVADs (CF-LVAD) and includes the following predictors of mortality: patient age, center volume, albumin, creatinine, and international normalized ratio (INR) [9•, 10•, 11•, 12•,]. The MELD-XI score, which includes sodium, creatinine, and bilirubin, with the exclusion of INR, has been validated in the CF-LVAD population as well [13•, 14•].

A review of the most recent INTERMACS report indicates that early after LVAD implant, multisystem organ failure, right heart failure, and strokes (ischemic or hemorrhagic) are the most common causes of mortality [2•]. Examining the risks for mortality after LVAD implant, these investigators identified older age, worsening cardiogenic shock (INTERMACS profiles 1–2) pre-LVAD, right ventricular (RV) failure necessitating RV assist device, and pre-implant dialysis requirement as the greatest risk factors driving post-operative mortality and morbidity. Female sex has also been reported as an early post-operative risk factor. Other identified risks include prior cardiac surgeries, presence of chronic obstructive pulmonary disease (COPD), and poor nutritional status.

The ideal approach to manage patients that present with IM profile 1 remains an area of active research. Amione-Guerra et al. performed a retrospective analysis of 244 patients implanted with a continuous flow (CF) LVAD. Patients were dichotomized at admission into low- or high-risk categories using a cutoff of Model for End-Stage Liver Disease (MELD) ≥ 19. Patients were then reclassified using the MELD classification at day of implant following treatment to stabilize those that remained at low risk, or worsened to high risk, or remained high risk, or improved to low risk. MELD score reclassification proved to be an independent and powerful predictor of mortality in sick patients undergoing LVAD implantation [15•]. Future research efforts should continue to be directed at identifying factors that attenuate the causes of early post-LVAD mortality, particularly multisystem organ failure, right heart failure, and stroke.

CF-LVAD as DT or BTT is most appropriate in select patients with an IM profile 1 that respond favorably to medical and short-term device therapy and in patients with IM profiles 2–4. It is important to anticipate higher operative risk in patients with the IM profile 1. Factors that impact post-operative morbidity and mortality and that have been defined as exclusion factors in major clinical trials are defined in Table 1. When considering a patient with contraindications to LVAD, the number of high-risk features is proportional to the risk of post-operative mortality, such that each center should decide the point at which a patient's LVAD implant risk becomes prohibitive.

LVAD characteristics and device-related clinical outcome

CF-LVAD pump design consists of a device inlet (inflow cannula), device outlet (outflow cannula), and a single rotating element, such as a rotor or impeller within a pump housing that propels blood forward by spinning the impeller at high speeds, designated as rotations per minute (rpm). The flow of blood generated by LVAD is directly proportional to the impeller speed and inversely proportional to the VAD differential pressure, further

Table 1. Select contraindications to LVAD implantation

Select contraindications to contemporary CF-LVADs
Life expectancy limited by non-cardiac condition to < 12 months
Presence of an active, uncontrolled infection
Intolerance to anticoagulant or antiplatelet therapies
Refractory severe end organ dysfunction or failure characterized by any of the following: • An international normalized ratio (INR) > 2.0 not due to anticoagulation therapy • Total bilirubin > 43 μmol/L (2.5 mg/dL), shock liver, or biopsy proven liver cirrhosis
History of severe chronic obstructive pulmonary disease (COPD) defined as the ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC) < 0.7 and FEV1 < 50% predicted
History of stroke within 90 days of LVAD implant
Significant peripheral vascular disease (PVD) accompanied by rest pain or extremity ulceration
Psychiatric disease/disorder, irreversible cognitive dysfunction, or psychosocial issues that are likely to impair compliance

defined as aortic pressure minus left ventricular (LV) pressure in mmHg. There are two rotary pump designs: axial versus centrifugal. HMII is an axial pump that utilizes an Archimedes' screw design in which the inflow of blood is parallel to the rotor axis of rotation. The HVAD and HM3 are centrifugal pumps in which the inflow of blood is perpendicular to the axis of rotation of the impeller.

Due to difference in engineering, each pump has its unique hydrodynamic properties (Table 2). The best representation of the relationship between VAD differential pressure and VAD flow is the head-flow (HQ) performance curve, where VAD differential flow is on the *Y*-axis and VAD flow is on the *X*-axis. It is generally understood that the pressure/flow characteristic of centrifugal pumps is flatter than that of axial pumps. In general terms, this means that the rate of change in head pressure (pump outlet minus the pump inlet pressure) with increasing flow (increasing pump speed) is less with a centrifugal pump like the

Table 2. Comparison characteristics of the HMII, HVAD, and HM3 pumps and speed testing recommendations

Device	Speed	Average speed	Flow	Intrinsic pulse	Pump speed adjustments and speed range testing
Heartmate II	6000–15,000 rpm	9400 rpm	Axial	No	400 rpm increments (8000 to 12,000 rpm)
HVAD	1800–4000 rpm	2800 rpm	Centrifugal	Optional Lavare cycle (200 rpm ramp down then up once/min)	100 rpm increments (2400 to 3200 rpm)
Heartmate 3	4800–6500 rpm	5400 rpm	Centrifugal	Yes (2000 rpm ramp down followed by 4000 rpm ramp up 30 times/min)	100 rpm increments (4600 to 6200 rpm)

HM3 and HVAD compared with the axial HMII pump. However, for small centrifugal pumps like the HM3 and HVAD, this is not so near the typical operating conditions. Furthermore, centrifugal pumps have greater hydraulic efficiency and can generate higher kinetic energy transfer at slower rotation speeds.

Additional engineering differences between the centrifugal LVADs distinguish the HM3 from HVAD. The HM3 features a fully magnetically levitated internal rotor, which allows greater distance between the rotor and the pump housing, creating larger gaps for blood flow. This design, along with the textured blood-contacting surface, minimizes blood trauma and improves biocompatibility [16•]. Additionally, the HM3 is designed with an "intrinsic pulse" whereby every 2 s, the rotor speed decreases by 2000 rpm from the set speed for 0.15 s and then increases by 4000 rpm for 0.2 s with the intention of preventing pump stasis and therefore thrombosis [17•]. This artificial pulse is asynchronous with the native heart beat and does not necessarily result in a palpable pulse.

The HVAD impeller is suspended by a combination of passive magnetic and hydrodynamic bearing systems and is notable for its small size, without a need for pre-peritoneal pocket [18•]. The HVAD can be implanted via lateral thoracotomy approach, sparing the sternum. HVAD programing has been recently updated with the option of the Lavare cycle, which can be turned on or off by the provider. The Lavare cycle is an algorithm that decreases the HVAD set speed by 200 rpm for 2 s and increases it by 400 rpm for 1 s. This 3-s cycle is set to repeat every minute [6••]. In comparison to the HM3, the Lavare cycle is not always used and the frequency of this built-in speed change algorithm is less.

Engineering differences between axial and centrifugal flow LVADs translate into meaningful clinical outcomes; however, there has not been a head-to-head comparison of the HM3 and HVAD. The MOMENTUM 3 trial compared axial flow pump HMII with the fully magnetically levitated centrifugal HM3 pump. The HM3 is much more hemocompatible than the HMII. The primary endpoint for the full cohort study was survival at 2 years free of disabling stroke (> 3 modified Rankin Scale) or reoperation to replace or remove a malfunctioning device. In the MOMENTUM 3 trial, HM3 met its primary endpoint and also demonstrated superiority to HMII. Survival at 2 years free of disabling stroke or reoperation to replace or remove a malfunctioning device was 74.7% for HM3 versus 60.6% for the HMII ($p < 0.0001$ by log-rank test). There were statistically significant reductions (versus the HMII) in suspected or confirmed pump thrombosis, stroke (including all types of strokes—hemorrhagic, ischemic, and disabling), and all types of bleeding (including gastrointestinal) [6••].

The ENDURANCE trial demonstrated non-inferiority of the HVAD versus the control (Heartmate II) with fewer device malfunction or thrombosis in patients with advanced heart failure ineligible for heart transplantation. However, stroke was more common in HVAD subjects [19••]. The ENDURANCE Supplemental trial was designed to prospectively determine effectiveness of a blood pressure management strategy to reduce neurological injury in patients receiving the HVAD System [5•]. This trial was a prospective, multicenter evaluation of 465 patients with advanced heart failure ineligible for transplantation, randomized 2:1 to HVAD ($n = 308$) or the control which was the HMII

($n = 157$). The primary endpoint was the 12-month incidence of transient ischemic attack or stroke with residual deficit 24 weeks post-event. The ENDURANCE Supplemental trial failed to demonstrate non-inferiority of HVAD versus HMII regarding the pre-specified primary endpoint. However, the trial confirmed that BP management remains critical in this patient population with enhanced BP control associated with significantly reduced stroke rates in HVAD subjects. Moreover, secondary composite endpoint of freedom from death, disabling stroke, and need for device replacement or urgent transplantation demonstrated superiority of the HVAD (76.1%) versus the HMII device (66.9%) ($p = 0.04$).

Regarding outcome data related to using the optional Lavare cycle in patients supported by the HVAD, there was a retrospective analysis of the Registry to Evaluate the HeartWare Left Ventricular Assist System (ReVOLVE registry). Two hundred and fifteen patients had the HVAD Lavare cycle programmed on compared with 33 that did not. There was a statistically significant lower incidence of stroke, sepsis, and right heart failure in those with the Lavare cycle on [20••]. Taken together, these findings implicate device-specific operational characteristics influence patient outcomes, particularly with respect to hemocompatibility-related adverse events (HRAEs).

Device pump speed optimization strategies

Despite being deemed clinically stable on continuous flow LVAD support, it is not uncommon for patients to have elevated ventricular filling pressures at baseline pump speeds. Uriel et al. demonstrated 57% of stable ambulatory patients supported by the HMII (pump speed 9094 ± 417 rpm) and HVAD (2704 $\pm$ 147 rpm) did not have both central venous pressure (CVP) and PCWP in the defined normal range (PCWP < 18 mmHg and CVP < 12 mmHg) [20••].

Hemodynamic optimization using echocardiographic ramp testing and right heart catheterization to measure intra-cardiac pressures and cardiac index over a range of LVAD speeds is well established [20••, 21•, 22•]. These types of studies have linked optimal hemodynamics on device support with improvement in symptoms, functional capacity, and a lower hospital readmission rate [23••, 24••, 25•,26•,]. Using echocardiography alone, Frea et al. demonstrated that patients on HVAD support that had optimal unloading defined as a normal estimated left atrial pressure (LAP) and right atrial pressure (RAP) assessed non-invasively had a lower risk of adverse cardiac events (composite of heart failure (HF) hospitalization, death, or urgent transplantation) at follow-up (OR 0.2, CI 95% 0.1–1.0, $p < 0.05$) when compared with the other profiles.

Uriel and colleagues recently demonstrated the important association of hemodynamic optimization while on HMII and HVAD support and HRAEs including non-surgical bleeding, thromboembolic events, pump thrombosis, or neurological events. Eighty-three stable outpatients underwent a hemodynamic ramp test to help select the pump speed that resulted in an optimal hemodynamic profile defined as achieving all three of the following: CVP < 12 mmHg, PCWP < 18 mmHg, and CI > 2.2 L/min/m^2. There were 2 primary findings. First, 1-year survival free of any HRAEs was achieved in 75% of the optimized group ($n = 51$) and in 44% of the non-optimized group ($n = 32$) (hazard ratio 0.36, 95% confidence interval 0.18–0.73, $p = 0.003$). This first

observation was driven equally by suppression of both bleeding and thrombotic events in patients with normal hemodynamics on CF-LVAD support. Second, the net hemocompatibility score, using 4 escalating tiers of hierarchal severity to derive a total score for events, was significantly lower in the optimized group than the non-optimized group (1.02 versus 2.00 points/patient; incidence rate ratio 0.51, 95% confidence interval 0.29–0.90, $p = 0.021$) [24•].

Echocardiography to detect non-optimal hemodynamics

Echocardiography plays an essential role in LVAD optimization [27•, 28••]. Echocardiographic parameters of utmost importance include the following: assessment of right ventricular (RV) function, position of the interventricular septum, left ventricular (LV) geometry, particularly the LV end-diastolic dimension (LVEDD), and presence and severity of valvular disease, particularly of the mitral and aortic valves. Factors that indicate adequate LV unloading include a reduction in mitral regurgitation severity and a reduction in LV size (e.g., left ventricular end-diastolic dimension). Ideally, the interventricular septum should be neutral (midline), suggesting an adequate balance of RV and LV filling pressures.

There are two published reports that validate the accuracy of echocardiography to detect intra-cardiac hemodynamics based on simultaneous right heart catheterization testing in patients supported by the HMII and HVAD [23••, 29••]. Estep et al. showed that several parameters, including mitral ratio of the early to late ventricular filling velocities > 2, RAP > 10 mmHg, systolic pulmonary artery pressure (sPAP) > 40 mmHg, left atrial volume index > 33 mL/m^2, ratio of mitral inflow early diastolic filling peak velocity to early diastolic mitral annular velocity > 14, and pulmonary vascular resistance > 2.5 Wood units, accurately identified patients with pulmonary capillary wedge pressure > 15 mmHg (area under the curve 0.73 to 0.98). An algorithm integrating mitral inflow velocities, RAP, sPAP, and left atrial volume index was 90% accurate in distinguishing normal from elevated pulmonary capillary wedge pressure (e.g., > 15 mmHg).

Frea et al. demonstrated that estimated right atrial pressure (eRAP) derived from the inferior vena cava (IVC), hepatic venous systolic filling fraction (HVFF), and right ventricular peak tricuspid valve E/e′ methods significantly correlated with invasive RAP ($r = 0.839$, $p < 0.001$). These investigators demonstrated their algorithm accurately detected a high left atrial pressure (area under the curve 0.91, $p < 0.001$) in patients supported by the HVAD. Although the focal points are different between these two recommended algorithms to detect partial LV unloading defined as an estimated pulmonary capillary wedge pressure > 15 mmHg, the established interplay between the LVAD and the LV and right ventricle is highlighted with the estimated RAP being an important component in both algorithms.

Using these detection algorithms can help identify patients supported by current generation LVAD at greater risk for adverse outcome including progressive heart failure (HF). For those specifically with predominately left-sided HF and/or biventricular HF, pump speed optimization after excluding occult hypertension and device-specific problems (e.g., rotor thrombus and hemolysis) is warranted. For those patients with

predominately RV failure, an increasing recognized profile, consideration to decrease to the pump speed to minimize excessive LV unloading and worsening RV failure would be a consideration. It would be reasonable for stable patients with a detected "optimal" hemodynamic profile based on echocardiography to maintain the baseline pump speed in addition to background medical therapy.

An LVAD ramp study utilizes these principles to determine optimal pump speed setting by starting at a certain speed and incrementally increasing the LVAD pump speed by 100 rpm in the HM3 and HVAD and 400 rpm in the HMII until the speed at which optimal hemodynamic parameters are met as long as there are no signs of excessive LV unloading defined as acquired suction events and/or RV dilation. LVAD ramp studies are also instrumental in making the diagnosis of pump thrombosis with pump malfunction and cannula malposition [30•, 31•, 32•,33•].

Right heart catheterization to define hemodynamics

Evaluation of hemodynamics via right heart catheterization remains the gold standard to provide objective metrics of RV function (central venous pressure, pulmonary artery pulsatility index, RV stroke work index), pulmonary artery pressure and assessment of adequate LV unloading (pulmonary capillary wedge pressure), and perfusion (cardiac output and cardiac index). Several observational studies have examined the role of ramp studies for LVAD optimization. Uriel and colleagues conducted the Columbia ramp study published in 2012 in which data from 39 patients with HMII LVAD who underwent a total of 52 ramp tests was prospectively collected [34••]. This ramp study collected LVAD parameters (set speed, pulsatility index, power, and flow), patient hemodynamics (HR, BP), and echocardiographic data (LVEDD, LVESD, AV opening, AI, mitral regurgitation (MR), RVSP) and explored perturbations in these parameters in the setting of VAD thrombosis.

In a cohort of 17 patients with destination therapy HVAD, echocardiographic guided ramp studies lead to speed changes in speed changes in 47% of patients and resulted in improved RV function as defined by fractional area change and strain at 3-month follow-up [35•]. The incorporation of 3D echocardiography for assessment of native LV function, which better defines LV rotational mechanics over conventional 2D echocardiography, may add additional value in LVAD optimization [36•]. Uriel and colleagues demonstrated the safety and feasibility of optimizing CVP and PCWP using ramp studies in 16 patients with HM3 [22•]. In this same cohort of patients, the addition of echocardiography indicated that increases in LVAD speed (and therefore LV unloading) are associated potentially with unfavorable alterations in RV size and interventricular septum positioning [37•].

RAMP-IT-UP, a prospective, multicenter, randomized, pilot study trial compared hemodynamic-echo guided ramp study with standard of care including the use of echocardiography to exam patients supported by the HVAD. Forty-one patients were randomized [38••]. The hemodynamic ramp group ($n = 22$ patients) experienced more medication changes and had numerically but not statistically higher event-free survival

(62% versus 46%, $p = 0.087$; hazard ratio 0.46, 95% CI 0.2–1.2), with numerically but not statistically significant lower events per patient year (p = 0.084). In addition, there were no significant differences comparing the in the 6-min walk or Kansas City Cardiomyopathy Questionnaire tests at 6 months. It is important to highlight that this study was a pilot study not powered to detect a difference in clinical outcome and the protocol did not mandate the use of a Doppler-based algorithm consistent with one of the aforementioned echocardiographic studies to detect incomplete LV unloading to guide medical management. Based on the available data, it is best to incorporate both a contemporary echocardiographic and an invasive hemodynamic protocol to screen for non-optimal hemodynamics in this patient population.

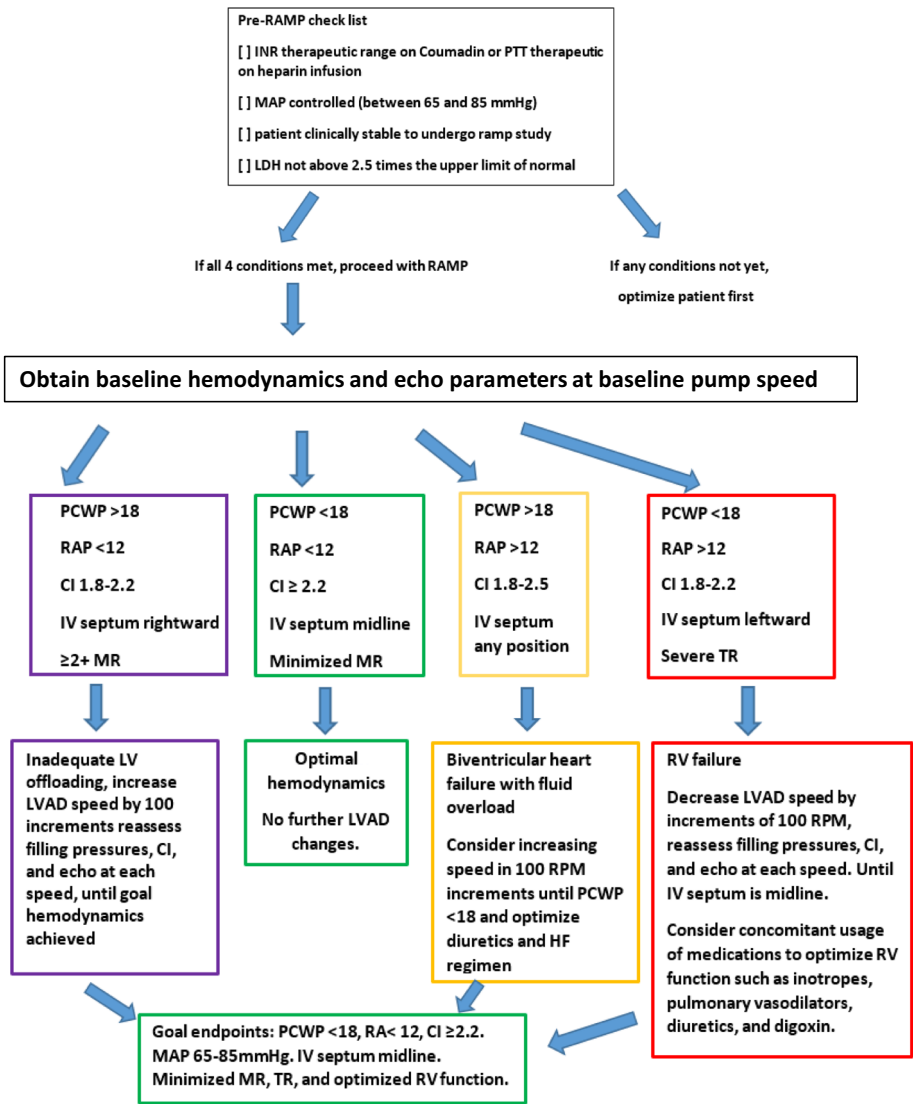

Fig. 1. Proposed HM3 and HVAD ramp study algorithm.

Protocol to optimize device function

The goal of device optimization is to ensure an underlying optimal hemodynamic profile based on the PCWP to RA relationship. Before pump speed changes are made, it is important to ensure adequate control of mean arterial blood pressure (65–85 mmHg) and adequate anticoagulation indices either on warfarin (INR 2 to 3) or on a heparin infusion (therapeutic PPT) prior to RAMP testing. Patients should also be hemodynamically clinically stable prior to the RAMP study. In addition to using surveillance echocardiography (e.g., transthoracic echocardiogram post-op 1 week, 1, 3, 6, 9, and 12 month, and every 6 months thereafter), RHC and echo should ideally be performed simultaneously in the catheterization lab with the following hemodynamic assessment: RAP, PAP and mean PAP, PCWP, and Fick cardiac output and index. Echocardiographic parameters should include interventricular septum position (midline, leftward shift, or rightward shift), degree of MR, LVEDD, AV opening status (opened every beat, intermittent opening, or persistently closed), and RV size assessment (Fig. 1). The endpoint of the study is defined by optimized hemodynamics: CVP < 12 mmHg, PCWP < 18 mmHg, and cardiac index > 2.2 with adequate mean arterial pressure, and absence of suction events or cardiac symptoms such as chest pain, dyspnea, palpitations, or dizziness.

For both HM3 and HVAD, acquiring hemodynamics and echo images at baseline settings is important. If speed changes are to be made, we recommend based on published reports increments of 100 rpm and waiting 3–5 min before recording hemodynamics at the new speed. If baseline filling pressures suggest inadequate LV unloading (PCWP > 18, RAP < 12, CI 1.8–2.2, septum rightward), increase the LVAD speed by increments of 100 rpm and record filling pressures and CI with echo documentation of the IV septum, MR severity, LVEDD, and RV size/dimensions at each speed. If baseline filling pressures suggest biventricular failure or volume overload (PCWP > 18, RAP > 12), consider increasing LVAD speed by increments of 100 rpm and concomitant medication optimization with diuretics. If baseline filling pressures suggest RV failure (PCWP < 18, RAP > 12, CI 1.8–2.2, IV septum leftward), consider decreasing LVAD speed by 100 rpm and concomitant use of diuretics and medications to optimize RV function until IV septum becomes midline with more favorable filling pressures. In the cases of severe biventricular failure or RV failure, it is reasonable to consider leaving the Swan-Ganz catheter secured in place for further optimization.

Conclusion

Improved LVAD engineering designs have led to significant improvements in biocompatibility with resultant reduction in HRAEs. The demand for LVAD therapy and its clinical applications is anticipated to continue to expand. Careful patient selection, utilization of detection algorithms that define non-optimal hemodynamics, and implementation optimization strategies remain of paramount importance to curb morbidity associated with the currently available LVADs.

Compliance with Ethical Standards

Conflict of Interest
Jerry D. Estep MD declares the following conflicts: Consultant for Abbott and Medical Advisor for Medtronic Inc.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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